PB80-169568

Health Effects Research Program Summary Report for Fiscal Years 1974-1978

MITRE Corp.
McLean, VA

Prepared for

Environmental Protection Agency
Washington, DC

Dec 79

U.S. Department of Commerce
National Technical Information Service
NTIS

United States
Environmental Protection
Agency

Office of Environmental Processes and
Effects Research
Washington, D.C. 20460

EPA-600/7-79-121
December 1979

Research and Development

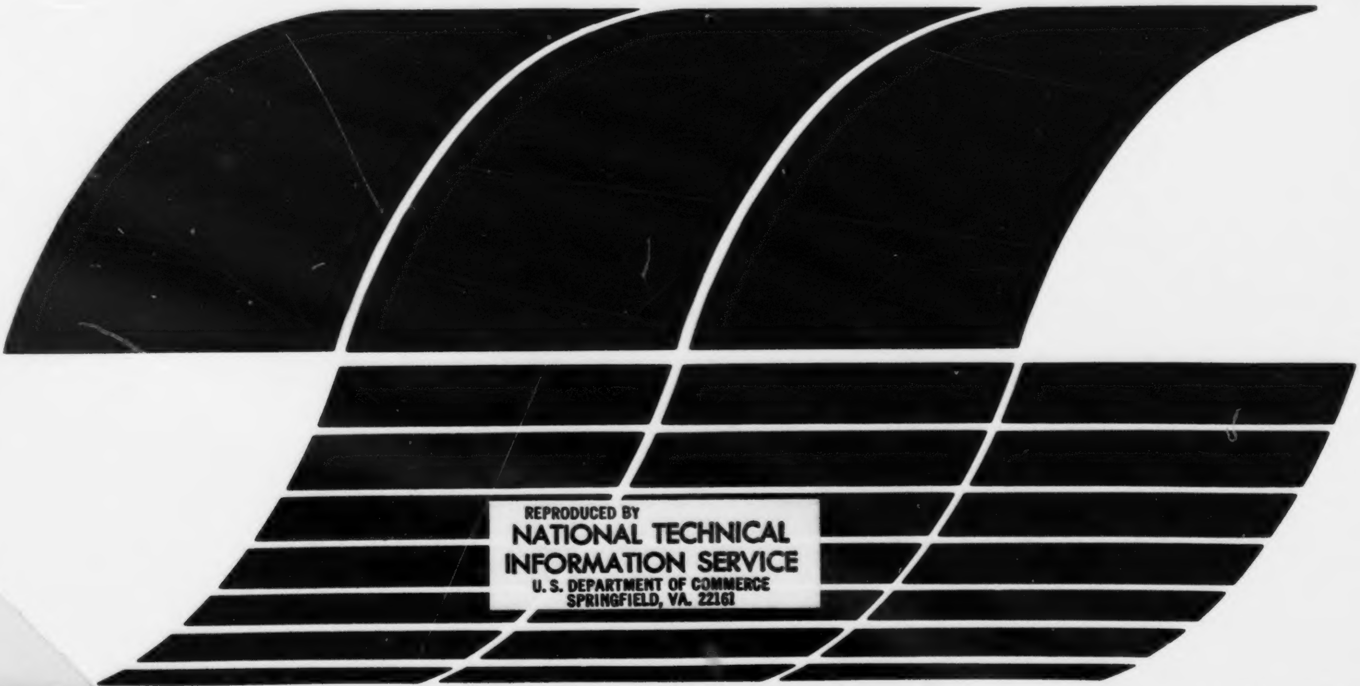
PB80-169568

EPA

Health Effects Research Program

Summary Report for Fiscal Years 1974-1978

Federal Interagency Energy/Environment R&D Program Report



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TECHNICAL REPORT DATA

(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA 600/7-79-121

2.

3. RECIPIENT'S ACCESSION NO. PB 80 169568

4. TITLE AND SUBTITLE
Health Effects Research Program--Summary Report For Fiscal Years 1974-1978

5. REPORT DATE December 1979

6. PERFORMING ORGANIZATION CODE

7. AUTHOR(S)
Richard D. Thomas, Alexis D. Taylor, Judith G. Gordon

8. PERFORMING ORGANIZATION REPORT NO. MTR 79W00100

9. PERFORMING ORGANIZATION NAME AND ADDRESS
The MITRE Corporation
Metrek Division
McLean, VA 22102

10. PROGRAM ELEMENT NO.

11. CONTRACT/GRANT NO. 68-01-5051

12. SPONSORING AGENCY NAME AND ADDRESS
U.S. Environmental Protection Agency
Office of Environmental Processes and Effects Research
Office of Research & Development
Washington, D.C. 20460

13. TYPE OF REPORT AND PERIOD COVERED Executive Summary 74-78

14. SPONSORING AGENCY CODE EPA/600/7

15. SUPPLEMENTARY NOTES
This project is part of the EPA-planned and coordinated Federal Interagency Energy/Environment R&D Program.

16. ABSTRACT

The Federal Interagency Energy/Environment Research and Development Program which is coordinated by the U.S. Environmental Protection Agency was initiated in the latter half of fiscal year 1974 to ensure that health and environmental problems related to energy resource development would be anticipated and evaluated. This document provides an overview of the Interagency-supported health effects research program from an administrative as well as various technical perspectives. In this updated program review, which is based on the individual task progress reports available for fiscal years 1974 through 1978, the research projects are reviewed and discussed according to King-Muir objectives and selected scientific discipline, biological endpoint, and agent/pollutant categories.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Ecology Environments	Ecological Effects Health Effects Energy Resource Development	97G

18. DISTRIBUTION STATEMENT
Release to Public

19. SECURITY CLASS *(This Report)* Unclassified

20. SECURITY CLASS *(This page)* Unclassified

21. NO. OF PAGES

22. PRICE

EPA Form 2220-1 (9-73)

EPA 600/7-79-121
DECEMBER 1979

FEDERAL INTERAGENCY ENERGY/ENVIRONMENT RESEARCH AND DEVELOPMENT PROGRAM

HEALTH EFFECTS RESEARCH PROGRAM
Fiscal Years 1974-1978
Summary

by

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FOREWORD

The U.S. Environmental Protection Agency (EPA) was established as a single organizational entity to administer federal environmental legislation. Such legislation requires EPA to protect and enhance the nation's environment through control and abatement of environmental pollution.

The Office of Research and Development is the principal scientific component of EPA. Its fundamental role is to produce the scientific data and technical tools needed to develop a national policy for effective control of environmental pollution through development of appropriate guidance or regulation.

This report presents a comprehensive summary to date of the results of energy-related health research funded by the interagency energy/environment program which is coordinated by the Energy Effects Division of the Office of Research and Development.

The objectives of this interagency research program are to provide the techniques and data necessary to: (1) determine the qualitative and quantitative effects of energy-related agents on human health; (2) assess the human health risks associated with all aspects of energy production and utilization; (3) provide guidance for energy systems-related control and abatement programs; and (4) provide reliable information requested for the establishment of regulations pertaining to exposures to energy-related agents.

ABSTRACT

The Federal Interagency Energy/Environment Research and Development Program which is coordinated by the U.S. Environmental Protection Agency was initiated in the latter half of fiscal year 1974 to ensure that health and environmental problems related to energy resource development would be anticipated and evaluated. This document provides an overview of the Interagency-supported health effects research program from an administrative as well as various technical perspectives. In this updated program review, which is based on the individual task progress reports available for fiscal years 1974 through 1978, the research projects are reviewed and discussed according to King-Muir objectives and selected scientific discipline, biological endpoint, and agent/pollutant categories.

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ACKNOWLEDGMENTS

This overview of the Federal Interagency Energy-Related Health Effects Research Program is an update of a previous summary review* that was prepared for the Office of Energy, Minerals and Industry within the Office of Research and Development of the U.S. Environmental Protection Agency (EPA) under Contract No. 68-01-3539. Some material from the previous report is incorporated in this document.

The support and helpful comments provided by Gerald Rausa, the EPA Project Officer, are gratefully acknowledged. The technical assistance of Rebecca Meadows and Yasuko Anglin and the editorial assistance of Pamela Miller are appreciated.

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*J. Dorigan and H. Mahar. "Health Effects Research Program, Fiscal Years 1975-1977, Summary." MTR-7630. The MITRE Corporation, Metrek Division, McLean, Virginia. August 1977.

SECTION 1

SUMMARY

Under the auspices of the Federal Interagency Energy/Environment Research and Development (R&D) Program, approximately 58 million dollars have been funded during the past four and one-half years to support health research efforts. The purpose of this research is to ascertain the potential health effects associated with this country's accelerated energy resource development. This document summarizes the continuing energy-related health effects R&D effort in a manner that succinctly conveys the status and direction of the Federal Interagency Energy-Related Health Effects Research Program to date.

More than 280 energy-related health effects research projects have been supported by the Federal Interagency Energy/Environment R&D Program since its inception. All of these research projects are discussed in this summary which is based on available project documentation, primarily the three-year summary reports. The accomplishments of the research projects in the program are reviewed from the perspectives of the King-Muir objectives and selected scientific discipline and biological endpoint categories. The program is reviewed from the perspectives of King-Muir objectives and selected scientific discipline, biological endpoint, and agent/pollutant categories.

The projects in the research program are listed in the Appendix.

SECTION 2

INTRODUCTION

Health and environmental problems arising from intensified domestic energy development and increased energy use are becoming increasingly important. As a consequence of the first oil embargo in 1973, the Chairman of the Atomic Energy Commission, Dixie Lee Ray, organized a committee to survey federal and private energy-related research activities and to recommend an energy research and development (R&D) program for the nation. Specific goals and recommendations were conveyed in the December 1973 report of the Ray Committee (The Nation's Energy Future). This report led to a special Congressional appropriation for environmental and health research related to energy development which ultimately resulted in the establishment of the Federal Interagency Energy/Environment R&D Program.

Two federal Interagency Working Groups* representing 23 departments and agencies were convened to ensure that major health and environmental problems related to energy resource development would be anticipated and evaluated on a schedule compatible with energy technology development and commercialization. These Working Groups developed the program structure for a federal interagency research and development effort that would assess potential health and environmental effects of accelerated energy development and would perfect pollution-control measures in order to minimize the associated environmental impacts. In addition, the Working Groups also defined specific goals and recommendations for the Federal Interagency Energy/Environment Research and Development Program.

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*The Interagency Working Group on Health and Environmental Effects of Energy Use and the Interagency Working Group on Environmental Control Technology for Energy Systems.

The Federal Interagency Energy/Environment R&D Program is administered and coordinated by the U.S. Environmental Protection Agency (EPA). Program monitoring was previously the responsibility of the Office of Energy, Minerals and Industry (now the Office of Environmental Engineering and Technology) within the Office of Research and Development, but this responsibility was recently assigned to the Energy Effects Division in the Office of Energy Processes and Effects Research (previously the Environmental Effects Division in the Office of Air, Land and Water Use). In order to maximize useful output, the program utilizes an extramural implementation approach, with EPA relying heavily on expertise available within other federal agencies. Research activities are performed by more than a dozen federal agencies in addition to EPA. The overall effort consists of two major parts:

- R&D on effects of pollutants, including health effects, ecological effects, pollutant characterization and measurement, pollutant transport and fate, and integrated assessment of all types of effects*
- R&D on technological measures for controlling the release of pollutants to the environment, including changes in the processes of energy extraction, conversion and utilization as well as end-of-system pollution-control measures**

The R&D program initiates research in order to develop the health and ecological effects data base that is needed to support environmental quality standards and source discharge regulations for energy technologies, many of which will not be commercially available before 1985 or 1990. The health and environmental effects component of the Federal Interagency Energy/Environment R&D Program incorporates an implementation strategy that addresses short-, intermediate-, and long-term research needs: the short-term need to support regulatory actions, the intermediate-term need to define the problem areas, and the long-term need to prevent, rather than merely to regulate, health and environmental damage. The criteria for determining research priorities include:

- the potential magnitude and importance of the health/environmental impacts
- the nature and potential utility of the technology

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*Described in the Final Report of the Interagency Working Group on Health and Environmental Effects of Energy Use (King-Muir Report), prepared for the Office of Management and Budget and the Council on Environmental Quality, November 1974.

**Described in the Final Report of the Interagency Working Group on Environmental Control Technology for Energy Systems (Gage Report), prepared for the Office of Management and Budget and the Council on Environmental Quality, November 1974.

- the expected rate of development/utilization of the technology

Within this framework, the R&D program must provide the clearest possible statement of the nature and extent of actual and potential changes in the human environment that will be associated with ongoing and proposed energy development.

Four federal agencies are participating in the health-effects component of the Federal Interagency Energy/Environment R&D Program--EPA, the Department of Energy (DOE), the National Institute of Environmental Health Sciences (NIEHS), and the National Institute for Occupational Safety and Health (NIOSH). The Federal Interagency R&D Program was designed with the base research program of each participating agency in mind; and, therefore, the additional funding from the Interagency Program (often referred to as the "EPA 'Pass-Through' Program") supports energy-related research that complements the existing research efforts of each participating agency. Health effects research areas not only reflect the current priorities assigned to the various energy technologies but also the perspectives of the participating agencies as defined by their legislative mandates.

The Federal Interagency Energy-Related Health Effects Research Program examines the health problems associated with fossil fuel combustion (both conventional and advanced), coal conversion, and energy conservation efforts. Problems associated with alternative energy sources are also being considered; some of the research effort is directed to generally applicable methods development and fundamental research.

This summary of the Federal Interagency Energy-Related Health Effects Program was limited by several constraints. The information used to prepare this document was derived primarily from three-year project summary reports. Other information sources that were used when necessary/available include project progress reports and quarterly, semiannual, annual and three-year project status reports. The number of reports available for each research project varied considerably, ranging from a general project description to a full complement of progress reports accompanied by publication reprints. These reports were prepared by the principal investigator, the project officer, and/or the program coordinator. The perspectives of the authors differed, and the type of information and the level of detail provided in the reports differed greatly.

This document provides a general overview of the Federal Interagency Energy-Related Health Effects Research Program from four perspectives. The more than 280 individual research projects that comprise the research program are reviewed and discussed from the perspectives of the King-Muir objectives and selected scientific disciplines, biological endpoints, and agents/pollutants.

This report is an update of and incorporates some material from a previous summary* that was prepared for the Office of Energy, Minerals and Industry within the EPA Office of Research and Development under Contract No. 68-01-3539.

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*J. Dorigan and H. Mahar. "Health Effects Research Program, Fiscal Years 1975-1977, Summary." MTR-7630. The MITRE Corporation, Metrek Division, McLean, Virginia. August 1977.

SECTION 3

SUMMARY OF ACCOMPLISHMENTS OF THE HEALTH EFFECTS RESEARCH PROGRAM

Many of the projects in the Interagency Energy-Related Health Effects Research Program are long term, and many were funded only recently. Nevertheless, it is possible to identify accomplishments that have been made to date. In this section, the accomplishments of the research program, as determined from the most recent reports available for the individual projects, are discussed from the perspectives of the King-Muir objectives, the scientific disciplines, and the biological endpoints of the research.

3.1 ACCOMPLISHMENTS REVIEW FROM THE PERSPECTIVE OF THE KING-MUIR OBJECTIVES

Each research project in the program was reviewed from the perspective of the five King-Muir objectives--Identification of Hazardous Agents; Dose and Damage Indicators; Metabolism of Hazardous Agents; Evaluation of Hazards to Man; and Damage, Repair, and Recovery Processes. The accomplishments and research findings within each category are discussed and summarized.

3.1.1 King-Muir Objective #1

Most of the efforts in this part of the program, the Identification of Hazardous Agents, were devoted to: developing new assay systems, adapting proven assays to specific needs, validating assays, determining optimum conditions, and establishing protocols for testing/screening samples. Two new mutagenicity/carcinogenicity screening techniques are adaptations of the Ames test--one allows liquid culture and the other is the well test that greatly reduces sample size. Other mutagenic assay systems that were developed include a multiple marker assay that uses Chinese hamster ovary (CHO) cells, an assay in which mutations are produced in mouse germ and somatic cells, a DNA-repair assay, and a bacteriophage system in which replication is inhibited. Methods developed for toxicity assays include the use of cellular ATP level as an early indicator of particle toxicity to rabbit alveolar macrophages (RAM) and an automated testing system to detect behavioral changes in monkeys. A new technique that may be useful in determining reproductive and teratogenic effects of energy-related substances is the automated, quantitative measurement of changes in sperm size and shape.

The energy-related products that have been tested include stack emission condensates from eastern and western coals; crude products and fractions thereof from coal gasification, coal liquefaction, and in situ retorting of shale oil; fibrous minerals; and various particulates. Efforts were devoted to obtaining, characterizing, fractionating, and preparing the test samples. For example, a cyclone system was developed that produces size-segregated particles, and methods were devised to prepare and to characterize specific particulate systems (e.g., metal oxides, pesticides, and fibrous amphibole minerals).

Samples are tested with the various assay systems in order to identify the hazards associated with these materials. Stack emissions condensates from combustion of eastern and western coal samples are being characterized and tested. It was determined that the different fractions of the various energy products differ in degree of hazard and that, for example, the basic fraction of Synfuel A-3 is the most mutagenic fraction. The chlorides and sulfates of various metals were ranked for toxicity to RAM cells: mercury, cadmium, and vanadium are most toxic; copper and zinc have moderate toxicity; and manganese and nickel are least toxic. In a study of the effects of simultaneous exposures to these compounds, it was found that the less toxic metals decrease the toxicity of the more toxic by competing for the same sites.

3.1.2 King-Muir Objective #2

The initial efforts in this part of the program, Dose and Damage Indicators, were also devoted primarily to developing assay systems and selecting appropriate test organisms/organs/cells. Some screening of energy-related substances was accomplished during testing of the assay systems.

Various assay systems were developed, improved, and/or tested for use in studies of the different harmful effects (carcinogenicity, mutagenicity, teratogenicity, toxicity) that can result from exposure to the energy-related substances. In work on assay systems pertaining to cell transformation, a bioassay system for transformation of lymphocytes was established, an improved method of scoring oncogenic transformations in mouse embryo cells was perfected, and cytochemical markers for cell transformation were developed. Progress was made in developing techniques for point mutation assays, multiple loci screening for mutations, and detection of inversions. Other test methods that were worked on include measurement of DNA repair, automatic screening for aberrant sperm, and a sulfite oxidase assay for detecting presence of sulfite in plasma after exposure to sulfur dioxide. A computer automated pattern recognition system for detecting and assessing neurobehavioral changes in monkeys is now complete and functional.

Other accomplishments are related to development of equipment, techniques, and test organisms. Some of the test systems required development of new equipment such as special tanks for long-term experiments involving exposure of fish to carcinogens. A method of providing slow release of test substances into experimental animals was perfected; tracheal implants of beeswax pellets that contain carbon particles coated with the chemical being tested are suitable for this purpose. New mouse strains were developed that have increased sensitivity to induction of point mutations. New cell lines were established in continuous culture (e.g., two human lymphocyte lines and a murine myeloma line) for use in specific assays.

Substances that were tested include: the effects of cadmium on spermatogonia and CHO cells; the effects of trace metals on pulmonary macromolecular metabolism, particularly with reference to enzyme inhibition and interference with collagen synthesis; the effects of lead on cultured liver cells (i.e., the mechanism of inhibition of heme synthesis) and on cell shape; and the effects of *in vivo* exposure of rats to sulfur dioxide on the immunoglobulin fraction of serum proteins and the amine levels in brain and plasma.

The foundations were laid for establishment of a National Environmental Specimen Bank. Material was selected for use in the sample containers; sample handling and preparation techniques were established; and analytical techniques were standardized.

A workshop was held on Screening Systems for Alternate Energy Effluents.

3.1.3 King-Muir Objective #3

The objective of research projects in this part of the program--Metabolism of Hazardous Agents--is to elucidate the mechanism of toxicity by examining routes of exposure to hazardous agents; by determining how these agents are incorporated, metabolized, and eliminated in/by various tissues and organs; and by studying the effects on tissues and organs and their functions. Many of the projects in this category were funded only recently, and it is therefore too soon to report on accomplishments.

In this category as in other parts of the research program, some of the initial work was devoted to developing and testing equipment and models that would be used in the research efforts. For example, equipment was developed and methods perfected for generation of ultrafine aerosols of ammonium sulfate and sulfuric acid for inhalation studies; metal aerosols were developed for *in vivo* and *in vitro* studies of lung metabolism; and a special aerosol sampling system for use in inhalation studies was designed, constructed, tested, and modified as necessary. An NMR spectrometer that has improved capabilities for characterizing bonding modes of organic and inorganic compounds is now operational. Equipment and techniques that have been developed for study of respiratory tract deposition include casts of the upper respiratory system and various aerosol deposition models. Computer simulation models for predicting body burden were completed for, e.g., lead. A carbon monoxide metabolism model accurately predicts absorption and elimination.

The effects of fly ash from coal combustion and coal gasification processes have been studied in ingestion as well as inhalation experiments. It was demonstrated that fly ash in the diet does not affect the metabolism and toxicity of cadmium, manganese, or mercury in rats. Loss in body weight that occurs when the diet contains 10 percent ash is greater in male than in female rats. Toxicity of fly ash particles on RAM cells in tissue culture is a function of particle size as well as composition (toxicity ranking in decreasing order is lead, nickel, manganese).

Respiratory tract deposition models have demonstrated that the primary mechanism of deposition is particle inertia in the nasal chamber. Use of casts of the upper respiratory system revealed a close correlation between aerosol deposition sites in specific airway branches and the observed sites of primary bronchial cancer.

The specific effects of some hazardous agents have been elucidated. Findings include, for example, that exposure to acid atmospheres *in vivo* decreases the rate of ciliary beating and alters the morphology of the tracheal epithelium. Selenium accumulates in liver, kidney, lung, gastrointestinal tract, blood, and bone and is cleared from internal organs in 10 to 35 days (half-time). Vanadium inhibits biosynthesis of unsaturated phosphatidyl choline and therefore would interfere with phagocytosis, the primary defense mechanism of the lung. Cadmium absorption is affected by the amounts of calcium and phosphorus present in the diet, and the rate of gastrointestinal absorption is age-related (greater in young than in old rats and guinea pigs). Exposure to microwave radiation for three months causes significant differences in serum electrolytes and rat behavior, differences that disappear after a one-month recovery period.

An Environmental Teratology Information Center was established. This data bank now includes 14,000 references and 3000 chemical agents that are listed by CAS number, molecular formula, synonyms, trade names, and generic name.

3.1.4 King-Muir Objective #4

In accordance with King-Muir Objective #4, Evaluation of Hazards to Man, most of the projects in this part of the research program are exploring the health effects of exposures to combinations of pollutants from energy-related processes and activities. The techniques used include *in vivo* and *in vitro* animal studies as well as epidemiological studies of exposed human populations.

Many of the studies examined the effects of various air pollutants, alone and in combination. These pollutants include particulates (fly ash, carbon particles, and metals), gases (sulfur and nitrogen oxides and ozone), and aerosols (acid mists).

It was found, for example, that inhalation of fly ash produces an immunosuppression response in the mouse and reduced lung and body weights in the guinea pig. Inhalation of a mixture of respirable carbon particles and acid mists causes greater adverse effects in the hamster than either of the individual pollutants, and exposure to the mixture reduces the ability of both hamsters and mice to resist respiratory infections.

Various epidemiological studies were initiated, and they are now in different stages of completion ranging from selection of subjects and design of questionnaires to data analysis. Several studies involve the general population, e.g., people exposed to air pollution in Chicago, to pollution from coal combustion in Cleveland, and to pollution from fossil fuel power generation in selected U.S. counties. Other epidemiological studies are examining health data on workers in various industries for correlation with industrial hygiene practices and occupational exposure to various pollutants that are energy-related.

In some of the projects, especially those that were funded more recently, accomplishments to date are primarily in the realm of initial preparatory work for the experiments. Different types of equipment (e.g., exposure chambers, aerosol analyzers, particulate monitors) were developed, calibrated, and/or evaluated. Some new experimental methods were developed and tested, e.g., a more sensitive method of determining mucopolysaccharide histochemically, a quantitative assay of monamine oxidase types A and B, the use of pica as a quantifiable behavioral assay of toxicosis, and a system for detecting inactive enzyme mutations and electrophoretic mobility mutations in the same loci. Statistical techniques were developed for low-dose extrapolation and for analysis of dose-response data.

Two air quality monitoring systems are now in operation after the component parts were evaluated, selected, and calibrated, and operation and maintenance procedures were established. The CHAMP system now includes mobile as well as stationary units, and data on air quality are being collected. A survey was conducted of the CLEANS/CLEVER system to develop a quality assurance system.

Various support projects are now in operation or in the final planning stages. The Chemical Repository for Alternate Energy Source

Material received 108 samples from five coal liquefaction or purification processes, two coal gasification processes, three shale oil recovery processes, and four coal combustion sources. The Repository then distributed 110 samples to 22 investigators for use in their research projects. Methodology was established for use by the National Environmental Specimen Bank in analysis of tissues and other samples. The Environmental Mutagen Information Center had 22,100 bibliographic entries in its information system as of March 1978 and 21,000 of these had been cross-indexed for rapid identification of the chemicals by CAS number, formula, generic and trade names, etc.

3.1.5 King-Muir Objective #5

King-Muir Objective #5--Damage, Repair, and Recovery Processes--is the determination of the damage, repair, and recovery processes in biological systems exposed to hazardous agents associated with energy technologies. With many of the projects in this part of the research program, initial efforts were devoted to preliminary work such as determining baseline data and developing equipment and assay systems. Various hazardous agents have been tested in animal systems (*in vivo* and *in vitro*) to ascertain the damage, repair, and recovery processes. In other projects, the emphasis was on immediate practical application of the findings through the development of health and safety guidelines for particular energy-related occupations and industries.

Determination of baseline data is essential so that adverse effects of hazardous agents can be recognized and quantified. Among the data ascertained so far are the normal values for immunochemistry in rats and hamsters, various baseline data for mouse lung tissue, and data on the histopathology, cell cycle kinetics, and ultrastructure of the hamster lung.

Special equipment, techniques, and assays were developed, tested, and/or calibrated or validated for use in some of the projects. Types of equipment include an ozone reaction chamber and a cell sorter for separating cell types involved in immune response. Among the specialized techniques developed in these projects are those for flow analysis, aerosol generation, *in vitro* stimulation of blastogenesis in hamster lymphocytes, preparation of nanogram samples of DNA by quantitative precipitation, and quantitative measurement of lead distribution in tissues by X-ray spectrometry. The assay systems that were developed or validated include an assay for immunologic competence, an enzyme activity test in pulmonary tissue, and the use of ethane and pentane as an index of lipid peroxidative lung damage.

The studies of the damage and repair processes induced by various hazardous agents are on-going, but some definitive findings have been reported. For example, during exposure to sulfur dioxide, ATPase activity in RAM cells is increased and the levels of intracellular and secreted lysozyme are reduced. Exposure of hamsters to nitrogen dioxide causes lesions in the terminal bronchiole area; multiple exposures induce fewer lesions than a single exposure, which may indicate an adaptive process. The fate of injected lead in mice depends on the compound (i.e., lead acetate or lead citrate); at physiological pH, lead citrate remains soluble in tissues whereas lead acetate is hydrolyzed and then taken up by reticuloendothelial tissues. Studies with marmosets demonstrated that polychlorinated biphenyls (PCBs) and dimethylhydrazine (DMH) affect the platelet-forming system; DMH causes thrombocytopenia whereas PCB causes thrombocytosis and anemia. The presence or lack of vitamin E in the diet has no effect on the phospholipid or fatty acid composition of mouse lung tissue, but high levels of dietary vitamin E reduce the ozone-induced changes in lung fatty acids. Dietary vitamin A is important in the repair of respiratory tract injury induced by nitrogen dioxide. The thiol compound WR-2721 provides protection against the adverse effects of cadmium, decreasing the mortality rate in rats exposed to cadmium oxide by inhalation (if it is administered just prior to the inhalation exposure) and reducing hemolysis of rat erythrocytes in saline containing cadmium oxide.

Two sets of health and safety guidelines that have been published are "Recommended Health and Safety Guidelines for Coal Gasification Plants" and "National Plan for the Safety and Health of Divers in Their Quest for Subsea Energy." A seminar was held on recirculation of industrial exhaust air; the objective of studies on this subject is the development of guidelines for exhaust air recirculation.

3.2 ACCOMPLISHMENTS REVIEW FROM THE PERSPECTIVE OF SCIENTIFIC DISCIPLINES

In the review of the Interagency Energy-Related Health Effects Research Program, the individual research projects were examined from the perspective of various scientific disciplines. This summary of program accomplishments is presented from the perspective of four scientific disciplines--Cellular Toxicology, Animal Toxicology, Human Health Studies, and Risk Assessment.

3.2.1 Cellular Toxicology

Research projects that involve study of the adverse effects of pollutants at the organ, tissue, cellular, and subcellular levels are classified under the scientific discipline of Cellular Toxicology. Many of the projects involve the respiratory system whereas others examine the effects of pollutants on the immune system and the reproductive system. Other projects are concerned with the subcellular level of activity (i.e., cell transformations and mutations).

Studies of the respiratory system use tissue cultures of lung and tracheae as well as alveolar macrophages to ascertain the effects of exposure by inhalation. In experiments using lung organ cultures, it was determined that many trace metals affect enzyme systems; for example, the synthesis of collagen is reduced as the result of enzyme inhibition by cadmium, copper, mercury, nickel, ruthenium, and zinc.

The rate of ciliary activity in epithelial cells of tracheal rings is not affected by carbon particulates but is decreased by exposure to sulfuric acid mist and to sulfuric acid mist combined with carbon particles. A tracheal implant system was developed that provides a useful technique for screening agents; it was found that both benzo(a)pyrene (BaP) and dimethylbenzanthracene (DMBA) induce hyperplasia in the epithelium and marked changes in the submucosa.

Cultures of RAM cells are being used to assess the toxicity of, for example, fly ash particles and various metals. It was found that particle size is an important factor in the toxicity of fly ash particles; the composition of the particle is also important with the toxicity of metals being (in decreasing order): lead, nickel, molybdenum. The RAM system was also used to determine the relative toxicities of various metal sulfates; they are (in order of decreasing toxicity): mercury, cadmium, vanadium, copper, zinc, manganese, nickel, sodium.

Most of the studies involving the immune system reported preliminary accomplishments. These include the establishment of lymphocyte cell lines from various mammalian species in continuous culture, development of techniques for reproducible cloning and stimulation of *in vitro* blastogenesis, and development of an assay for immunologic competence.

In studies of the effects of agents on the reproductive system, it was found, for example, that CHO cells concentrate cadmium which stimulates the production of M-RNA polysome (whereas it is decreased by exposure to X-ray). A multiple marker assay for mutagens that uses CHO cells has been developed. Tissue cultures of endometrial cells are being used to explore the effects of hormones on chemical carcinogenesis; it was found that progesterone conveys protection when it is added to the culture medium simultaneously with DMBA, but the cytotoxic effect is increased when progesterone is added first.

A variety of cell lines and tissue cultures are used in other studies. For example, cultured brain cells were used to ascertain the effects of lead on the offspring of pregnant rats administered lead in drinking water; the level of glycerol phosphate dehydrogenase was suppressed in pup brain cells. Rat liver cell lines were developed for use in the study of induction of metallothionein by heavy metals. Lead-resistant and cadmium-resistant rat cell lines (e.g., liver, glial cells) were isolated that will be valuable for the study of metal toxicity. It was confirmed that the 7,8-dihydro diol 9,10-epoxide of BaP, a mutagen, is a major metabolite of BaP in a variety of cells and tissues.

Achievements relating to carcinogenesis have been primarily in the realm of technique and assay development and validation. Techniques that were developed include an improved method of scoring oncogenic transformations in mouse embryo cells, plating techniques for transformed cells, a microfluorophotometry method for analyzing single cells and a flow cytometry technique to distinguish between normal and transformed cells. It was found that when suspended rat hepatocytes are treated *in vitro* with carcinogens, the number of binucleate cells decreases while there is an increase in the number of mononucleate cells.

Much of the progress in the work on mutagenesis is also related to the development of techniques and assay systems. The Ames test has been modified in various ways to meet particular needs (e.g., a "well test" that greatly reduces sample size and a liquid culture method that was used to analyze mutagenic urinary metabolites of carcinogens). Conditions were established for a liver cell mutagenesis assay in continuous rat liver cell lines. The sensitivity of a multiple loci screen for mutations in mammalian cells was validated by examining clones exposed to ultraviolet light. An assay system was developed which is based on the induction of inactive enzyme mutations and electrophoretic mobility changes in the same loci in two inbred mouse strains. New mouse strains were developed for use in studies of induction of point mutations. Air samples from various sites were tested for mutagenicity. In tests of specific substances, it was found that six synthetic fuel oil samples had no significant mutagenic activity; cyclophosphamide increases the rate of chromosome aberrations in six human lymphoid cell lines; and the mutagenicity of fluorene compounds is inhibited by other fluorene compounds.

Some of the research projects pertain to DNA damage and repair. The induction of unscheduled DNA synthesis in mouse germ cells provides an *in vivo* assay for DNA repair. DMBA does not induce unscheduled DNA synthesis in males; furthermore, BaP binds to sperm heads and to liver DNA. Of 15 carcinogens tested, 3 induce unscheduled DNA synthesis directly and 8 require prior metabolic activation. Lead and mercury induce base error into DNA. Ultraviolet and near-ultraviolet light differ in their effects on DNA damage and repair. A method of quantitatively preparing small samples of DNA was developed that should be able to provide material for direct studies of DNA.

In some of the projects, special equipment, techniques, and assays were developed. For example, a cyclone system for producing large quantities of size-segregated particles was calibrated. Automated flow systems were adapted to provide single-cell suspensions from hamster lung epithelium by lavage. An ozone reaction chamber for cultured cells was constructed and tested. Methods involving assays of enzyme activity and electron microscope examination were developed for assessing toxicity in cultured RAM cells. An RAM assay system was developed that is based on the cellular ATP level as the earliest indicator of particle toxicity.

3.2.2 Animal Toxicology

In animal toxicology studies, animals are exposed *in vivo* to hazardous agents in order to ascertain the effects of the exposure. The test animals are usually mammals although bacteria, insects, and fish are also used. In most of these research projects, the route of exposure was inhalation, the principal means by which man is exposed to energy-related agents, while in other projects the route of exposure was ingestion or injection. In some studies, exposure was to physical agents such as radiation.

Inhalation studies include exposures to fly ash and other particulates and to various gases and mists. It was demonstrated that fly ash inhalation increases lysozymic and protease activity in guinea pigs, causes an immunosuppression response in mice, and results in deposits of granular dust in the alveoli, subpleural and peribronchiolar lung areas in hamsters. In studies of inhalation of metal aerosols, it was found that: the most common atmospheric forms of selenium are readily soluble in biological fluids, and selenium accumulates in liver, kidney, lung, gastrointestinal tract, blood, and bone; vanadium inhibits the biosynthesis of unsaturated phosphatidyl choline and therefore would interfere with phagocytosis, the lung cells' primary defense mechanism; and cadmium chloride causes severe damage to lung tissue and enzymatic responses in the airways. When mice and hamsters were exposed to respirable carbon particles and/or acid mists and infectious agents, it was found that the pollutant mixture had a greater effect than either of the individual pollutants and that exposure to the mixture decreased resistance to respiratory infection.

Inhalation of sulfur dioxides causes a temporary increase in ATPase activity, alters the immunoglobulin function of serum proteins, changes amine levels in brain and plasma, and decreases the rate of ciliary beating. Both sulfates and sulfites are cleared rapidly from the respiratory system, with the clearance rate for sulfates being greater; prior inhalation of ferric oxide retards bronchial clearance initially and then accelerates it. Inhalation of sulfur dioxide or crude air particulate changes the rate at which BaP is metabolized in the lung. Inhalation of nitrogen dioxide increases the rate of mitosis in alveolar macrophages, the surfactant level in the lung, and the level of pulmonary phosphatidyl choline. Dietary vitamin A is important in the repair of respiratory tract injury induced by nitrogen dioxide inhalation. Inhalation of ozone causes lung damage, the extent of which is age-related (older rats, for example, are more susceptible) and also enhanced by lack of dietary vitamin E; another effect of ozone is decreased rate of bacterial ingestion by alveolar macrophages. Many of the effects of inhaled nitrogen dioxide and ozone are similar; for example, both cause a temporary increase in metabolic activity that disappears after a recovery period. After rats were exposed to aerosolized lead nitrate, distribution studies determined that lead is absorbed very rapidly from the lung--about 65 percent of the lead is located in the gastrointestinal tract within 6 hours after exposure and is then excreted in the feces within 24 hours; lead is cleared rapidly from soft tissues but accumulates in bone.

In most of the studies of metal toxicity, the substances were administered by ingestion or injection. The function of metallothionein in heavy metal metabolism is being investigated, and the time course for induction of metallothionein and chelation in rat liver in vivo was studied for cadmium, copper, and zinc. In studies of cadmium toxicity, it was determined that the rate of absorption depends on the levels of calcium and phosphorus in the diet and also on the age of the animal (being greater in the young); cadmium stimulates the movement of iron into serosal fluid; and cadmium is bound by serum proteins. The age factor in susceptibility was elucidated in various experiments with lead. Lead injected into pregnant rats is maternal- and embryotoxic, causing hemorrhage in the central nervous system and the fetoplacental unit and teratogenesis. Lead acetate fed to rat pups from birth induces lead encephalopathy whereas lead carbonate fed to 18-day-old rats causes toxic effects but no encephalopathy.

Various organic compounds were also administered by ingestion or injection in order to ascertain their effects. It was found, for example, that when BaP is administered at the maximum tolerated dose, it reduces the mating ability of male mice and causes females to produce fewer litters with fewer mice per litter. Dose-dependent vertebral abnormalities and reduced birth weight in mice are also effects of BaP. The effects of PCBs were studied in different animals. The ability to metabolize PCBs varies with the animal species (it is greater in the dog than the monkey or rat) and the molecular structure of the compound. Tetrachlorobiphenyl is fetotoxic, teratogenic, and neurotoxic in mice. Marmosets are particularly sensitive to PCBs and DMH, both of which affect the platelet-forming system, the former inducing thrombocytosis and anemia and the latter thrombocytopenia. Other organic compounds were also studied. Hexabromobiphenyl adversely affects mice and rats, depressing body weight, open field activity, forelimb grip strength, and reflexes. Dipterex has teratogenic effects, the severity of which varies with the species (rat > hamster > mouse). Synfuel and its fractions cause dominant-lethal mutations in mouse oocytes and spermatozoa.

The effects of electric fields were studied in different species. A DC electric field induces a sex-linked lethal mutation in male *Drosophila* and frameshift mutation in *Salmonella* TA-98, and confers upon *Photobacterium fisheri* the ability to grow in the presence of normally inhibitory concentrations of tetracycline. Sixty-hertz electric fields have little effect on rats, but sinusoidal electric fields decrease calcium efflux from cerebral tissue. Exposure to microwave radiation (918 MHz) induces biochemical and behavioral changes in rats that disappear after one month of recovery.

Many of the projects in this category, as in the other categories, required preliminary work. Exposure chambers and techniques for generating and characterizing aerosols were developed for the inhalation experiments. A computer-automated pattern recognition system for detecting and assessing behavioral changes in monkeys was completed and is now functional. New and improved assay methods that were developed include quantitative determination of monamine oxidase Types A and B, histochemical determination of mucopolysaccharide with increased sensitivity, automated quantitative determination of aberrant sperm cells, and a mouse oocyte system that is a good monitor of chemical toxicity because it is a highly sensitive *in vivo* system.

3.2.3 Human Health Studies

The projects in the Human Health Studies category are all directly related to the effects on human health of energy-related agents. Most of the projects involve epidemiological studies of general populations exposed to air pollutants or of workers exposed occupationally to energy-related agents. Some of the projects pertain to industrial hygiene studies and the development of safety and health guidelines for various energy-related industries. Other projects are more general in nature, being concerned with model development and the establishment of national information centers.

One experiment with human subjects was a study of the effects of exposure to nitrogen dioxide at rest and during moderate exercise. There were no physiologically significant changes in cardiovascular, metabolic, or pulmonary function that were attributable to nitrogen dioxide exposure.

Epidemiological studies of general populations exposed to air pollution from fossil fuel power generation are in progress in

Chicago, Cleveland, and selected U.S. counties. Air monitoring stations are in operation, the subjects are undergoing medical tests, and health and emissions data are being collected and analyzed. The CHAMP air quality monitoring system was developed and placed in operation. The CLEANS/CLEVER system is also operating, and a survey of the quality assurance system was conducted.

Various epidemiological studies have been started of workers occupationally exposed to energy-related agents. These include studies of workers at TVA coal-fired power plants and oil shale workers as well as workers in nonenergy industries who were exposed to nitrogen oxides, sulfuric acid, ozone, and various mineral fibers (e.g., mineral wool, clay fiber, attapulgite clay, and fibrous glass). Study groups have been selected, medical examinations administered, and data collected; these efforts as well as data analysis are continuing.

Several of the research projects are concerned with the working environment and industrial hygiene at different energy-related facilities. Information on coal gasification and liquefaction facilities and on other energy technologies (oil shale, tar sands, geothermal, solar, nuclear, and electric power transmission) was collected by literature searches and site visits. Medical and operating standards for divers were published, and work practices were recommended to protect Alaskan pipeline workers from cold stress and to provide for the occupational safety and health of workers in coal gasification pilot plants. In work on the recirculation of industrial exhaust air feasibility studies were completed, a seminar was held, guidelines are being developed, and in-plant evaluation has begun.

Progress was made in developing a method of using teeth as indicators of human exposure to toxic elements. More than 1500 teeth have been collected and analyzed and correlation analysis of environmental data, case histories, and chemical analysis data was started.

Various models have been developed that are now in different stages of testing and validation. These include respiratory tract deposition models, the trumpet model of aerosol deposition, and casts of the upper tracheobronchial tree. These models have demonstrated that the primary mechanism of aerosol deposition is particle inertia in the nasal chamber, that air mixing can occur in the deep lung, that aerosol concentrations in the airway and alveoli differ, that electrostatic charge enhances the deposition of smaller particles, and that there is a close correlation between deposition sites in specific airway branches and the observed locations of primary bronchial cancer. Some computer simulation models for body burden have been completed, including those for lead and the alkaline earth metals. A carbon monoxide metabolism model accurately predicts absorption and elimination.

The Environmental Teratology Information Center was established; as of February 1979, the system contained 14,000 references and listed 3000 chemical agents. The Environmental Mutagen Information

Center contained 22,100 bibliographic entries as of March 1978. In both information systems, chemicals are listed by CAS number, molecular formula, generic name, synonyms, and trade names.

3.2.4 Risk Assessment

The projects in the Risk Assessment category involve statistical and modeling techniques that are used in the estimation of risks associated with energy processes and energy-related agents, individually and in combination. Progress was made in developing and testing these methodologies.

Statistical methodology based on the Armitage-Doll multistage model for carcinogens was developed. When this methodology was used to analyze dose-response data from animal experiments, it was found that the response curves for most carcinogens are essentially linear at low dose levels.

Other efforts were devoted to the development of statistical and modeling techniques for estimation of the public health hazards associated with energy technologies. These techniques can also be used to evaluate alternative approaches to the question of competing risks.

3.3 ACCOMPLISHMENTS REVIEW FROM THE PERSPECTIVE OF BIOLOGICAL ENDPOINTS

Each research project in the Interagency Energy-Related Health Effects Research Program was reviewed from the perspective of the biological endpoint. The research findings are summarized below for each of the following endpoints: Carcinogenesis, Mutagenesis, Teratogenesis, Dysfunction: Physiological Damage, Dysfunction: Metabolic Effects, Dysfunction: Cytotoxic Response, and Morbidity/Mortality.

3.3.1 Carcinogenesis

Much of the effort in carcinogenesis research has involved the identification of morphological, cytological, and biochemical changes that lead to neoplastic cell transformations. Morphological transformations which lead to tumorigenic response have been identified for a number of mammalian cell lines. For example, research has identified the histological changes in lung tissue that lead to an increased incidence of tumors following multiple exposures to carcinogens combined with irritating mists and gases. The morphological transformations are being correlated with alterations in cell biochemical pathways.

The tumorigenic potential of many energy-related substances has been determined. For many substances, testing required the development of new techniques, laboratory equipment, and model testing systems. The new testing systems developed have specific genetic characteristics that are ideally suited for carcinogenicity screening.

3.3.2 Mutagenesis

There is considerable overlap in the research efforts on carcinogenesis and mutagenesis. As in carcinogenesis, much of the work in mutagenesis has led to the development of new model test systems. Current test systems have been validated, and multiple loci test systems have been developed. A major problem in testing industrial products and wastes is their complexity. Through newly developed fractionation procedures, crude industrial samples can now be screened for mutagenic potential with reliability. The components of many complex mixtures have been chemically identified. The mutagenic activity of many crude mixtures has been found to correlate with the mutagenic potential of individual components. Mutagenic synergism has been recognized for a few complex mixtures, though for most mixtures the subfraction activity is approximately additively equal to the total activity for the whole mixture.

Baseline data have been established for cytogenic aberrations (e.g., translocation, deletion, inversion, sister exchange) in a number of cell lines (e.g., human lyphoid, Escherichia coli, CHO, Syrian hamster embryo, rat hepatocyte). Validation of these cell lines for selective mutagens has been completed. A few testing techniques (e.g., heritable translocation test and the Ames test) have been integrated to provide for more efficient testing procedures.

3.3.3 Teratogenesis

Baseline information is being collected concerning the types of damage observed during periods of differentiation in developing embryos that are caused by exposure to energy-related agents. As with other types of toxic effects, some animal species are more sensitive to teratogenic damage than others. For example, sensitivity to the teratogenic potential of dipterex decreases in the following order: rat, hamster, mouse. In addition to pronounced and distinct abnormalities in the newborn, other features such as sternal variation, reduction in birth weight, and mortality in newborn are being correlated with exposure. The factors influencing cross-placental transfer of such agents as metallic pollutants are being determined. The distribution of lead over time in the fetus and the placenta of laboratory animals has been determined.

Chromosomal aberrations in mouse germ cells induced by coal conversion products have been determined. Some carcinogenic agents are toxic to oocytes. 3-Methylcholanthrene is a powerful mouse oocyte toxin. A number of agents have been tested for mouse oocyte killing activity. The mouse oocyte system is highly sensitive to toxic substances, and it can now be used for comparison with other, *in vitro* test systems for screening toxic substances.

Another new test examines sperm for shape abnormalities. Many energy-related agents have been tested in hamsters, mice, and rabbits by screening for abnormal sperm shape. New automatic quantitative techniques have been developed for measuring these abnormalities. The ability to measure sperm size has greatly improved the sensitivity of the sperm assay. Changes in size are found at concentrations well below those that would induce shape abnormality.

3.3.4 Dysfunction: Physiological Damage

Since the lung is a major route of exposure to toxic chemical agents, much research has focused on lung damage mechanisms. New test systems have been developed to screen toxic materials for lung damage potential. An *in vitro* model uses tracheal rings to measure the effect of agents on ciliary escalator action, an important upper respiratory tract clearance mechanism. Molybdenum, barium, and lead, and chromium sulfate do not affect this clearance mechanism; however, mercury, zinc, nickel, manganese, and cadmium cause considerable damage to the ciliary function.

An infectivity test uses mice and hamsters to screen toxic agents for their potential to hinder resistance to disease. Sulfuric acid mist and carbon particulates both reduce the animals' ability to resist respiratory infection.

Work has been completed on theoretical computerized models to predict aerosol depositions in various parts of the lung. The models are able to predict particle deposition efficiencies and patterns in the human nasal passages, tracheobronchial tree, and alveoli. There is a close correlation between aerosol deposition sites in specific airways and the observed locations of primary bronchial cancer.

In testing the neuro- and behavioral toxicity of energy-related agents, an automated behavioral testing system for monkeys has been developed. It is a computerized, automated pattern recognition system using television cameras. The "seeing computer" is more reliable than trained observers in scoring behavior after agent exposure.

3.3.5 Dysfunction: Metabolic Effects

Extensive metabolic studies are being conducted on the effects of trace metals including their effects on the biosynthesis of pulmonary connective tissue. A number of metals inhibit enzymes, thereby causing severe toxic effects. For example, lead is strongly toxic in the lung because it inhibits creatine phosphokinase by irreversibly binding to the enzyme. The structure of the enzyme is then drastically altered. This type of biochemical reaction, which interferes with collagen synthesis in lung organ cultures, provides a new sensitive biochemical tool for the *in vitro* evaluation of the toxicity of pollutants by monitoring collagen levels in organ cultures.

The metabolism of a number of energy-related agents in various laboratory animals has been determined. Their metabolism in some animals differs from that in others. The rate of metabolism can also differ among species. For example, the dog metabolizes PCBs better than either the monkey or the rat. This has important implications with respect to the monkey's susceptibility to cancer.

In the *in vitro* test systems, care must be taken to ensure formation of the proper metabolites of the agents being tested.

In many instances, the metabolites are carcinogenic and the original test material is not. A principal carcinogenic metabolite of BaP was isolated from Syrian hamster embryo cells, in vitro bovine and human mucosa incubations, mouse 10T 1/2 cells, and in vivo human skin. New in vitro cell lines were developed that have the ability to metabolize potential carcinogens to active metabolites.

Age plays an important role in metabolism. The ability of younger animals to metabolize toxic substances is quite different from that of older animals. Younger animals absorb much larger amounts of many substances from the gastrointestinal tract than older animals. There are also differences in the metabolism of various chemical forms of a substance. When both lead acetate and lead citrate were injected into mouse tissues, there were considerable differences in the deposition rates of the two compounds.

The metabolism of cadmium chloride, chromium, selenium, and vanadium in the lung was determined. At the same time, mechanisms of toxicity have been clarified. Vanadium inhibits the biosynthesis of unsaturated phosphatidyl choline; this interferes with phagocytosis, hindering the lung cells' primary defense mechanisms. Cadmium chloride causes acute inflammation and severe damage to lung tissue, disrupting enzymatic mechanisms in the lung airways. The competing nutritional factors affecting cadmium uptake were determined. The rate of gastrointestinal absorption of cadmium in the rat and guinea pig is age-related. Transport studies of cadmium and lead show that lead intoxication disrupts the transport of calcium at the blood-brain tissue barrier (choroid plexus). Calcium is necessary for proper nerve function.

3.3.6 Dysfunction: Cytotoxic Response

The cellular toxicity of metallic sulfates was determined using RAM cells and human lung fibroblasts. The most toxic metals--as determined by these two *in vitro* models--are mercury, cadmium, and vanadium. Copper and zinc have moderate toxicity, and manganese and nickel have low toxicity. Many metals seem to compete for the same sites of toxic action. Modifications in toxicity were observed when combinations of metals were added to cell cultures. For example, vanadium toxicity is reduced when copper sulfate is added. Zinc sulfate reduces cadmium sulfate toxicity, and sodium selenite protects against the toxicity of both cadmium sulfate and mercury sulfate. Some metals also increase fibrous collagen in human lung fibroblasts while others produce severe morphological changes in the macrophages.

The effects of cadmium on the karyotype stability of CHO cells is being investigated. CHO cells exposed to nontoxic levels of cadmium seem to become more resistant to its toxicity. Some metal salts and oxides are more soluble than others and therefore can be more toxic; however, some are not toxic because they are not soluble in the culture media or are not able to penetrate the cell wall.

In cytogenetic studies of lung cells, the epithelial cells lining small airways and alveoli showed greater susceptibility to nitrogen dioxide injury than cells lining bronchi or tracheae. Nitrogen dioxide stimulates lung cell and alveolar macrophage division in hamsters; however, no chromosome aberrations were induced at the levels used for exposure.

3.3.7 Morbidity/Mortality

Many of the studies examining morbidity and mortality as an endpoint are new research projects that have not yet produced results. Those projects that have been active for a longer period have identified and assembled the necessary personal health and medical records and have identified the cohort populations to be examined in the studies. In a few, data analysis is currently being completed and results should be reported soon.

SECTION 4

PROGRAM REVIEW FROM THE PERSPECTIVE OF KING-MUIR OBJECTIVES

The Federal Interagency Energy/Environment R&D Program was originally established to address the objectives defined in the King-Muir Report. The health effects research program component of the total R&D program is reviewed in this section from the perspective of the five King-Muir categories. These correspond to the five objectives defined in the King-Muir Report, namely:

Objective #1: Identification of hazardous agents--to utilize simple, inexpensive and reliable biological assay systems to detect the presence of toxic, carcinogenic, mutagenic, and/or teratogenic agents associated with energy-related activities.

Objective #2: Dose and damage indicators--to develop more rapid and sensitive biological methods to detect and quantify early, sublethal, reparable changes in various target organs or systems.

Objective #3: Metabolism of hazardous agents--to define the routes and rates of incorporation, metabolism, deposition and elimination of hazardous agents in order to specify tissues, organs, and functions at risk.

Objective #4: Evaluation of hazards to man--to quantitatively evaluate short- and long-term hazards to man (normal, susceptible and stressed populations) through simultaneous exposures to combinations of stresses associated with energy activities.

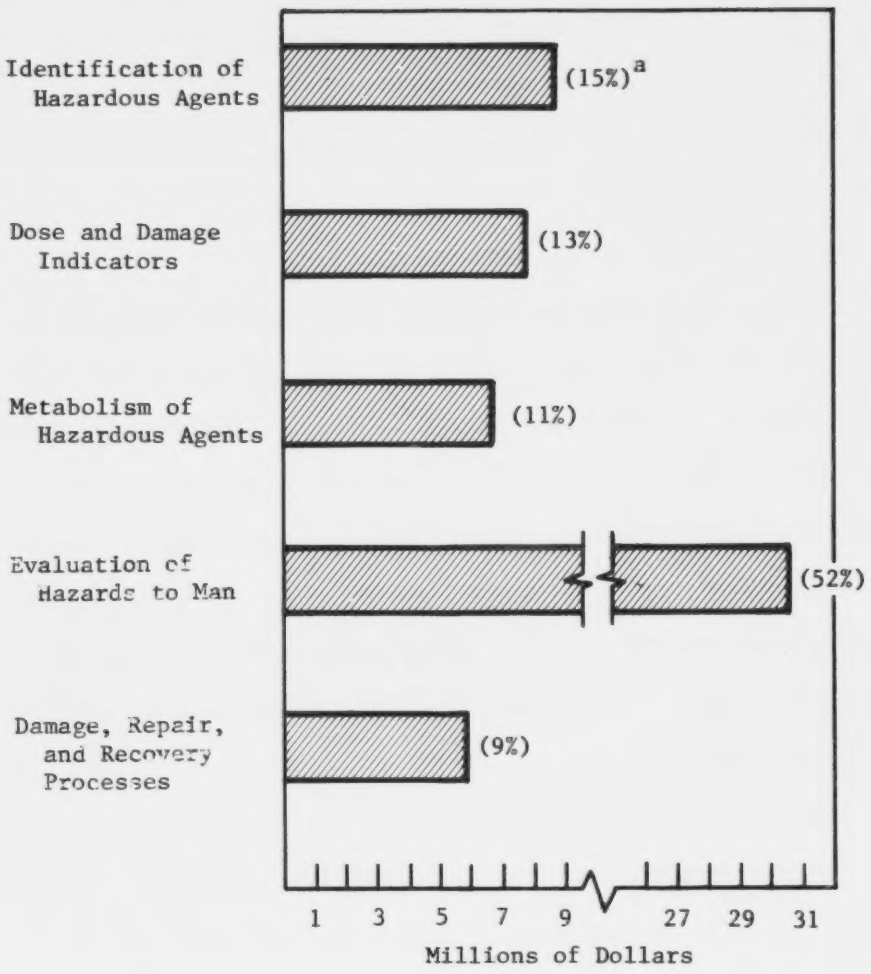
Objective #5: Damage, repair, and recovery processes--to determine the processes of damage, repair, recovery, protection, and amelioration in biological systems exposed to hazardous agents associated with energy technologies.

The funding provided each King-Muir category through fiscal year 1978 is indicated in Figure 1.

4.1 IDENTIFICATION OF HAZARDOUS AGENTS

Research that is being performed for King-Muir Objective #1, Identification of Hazardous Agents, involves the use of existing and new biological screening and testing systems to determine the presence of carcinogenic, mutagenic, teratogenic, and physiologically or metabolically toxic agents associated with energy technologies. Research projects in this category are concerned with identifying the specific fractions or subfractions of energy-related products, aqueous effluents, and atmospheric emissions that are responsible for toxicologic effects.

The various biological screening and testing systems that are used include microbial assays (e.g., Ames test), *in vitro* studies using specific cell lines (e.g., Chinese hamster ovary cells) or tissue cultures (e.g., rat hepatocytes), and *in vivo* studies (e.g., rat intratracheal studies and golden hamster inhalation studies). The purpose of these studies is to detect biochemical alterations, metabolic changes, cellular toxicity, carcinogenesis, mutagenesis, teratogenesis, system dysfunction (e.g., pulmonary effects), and/or



[a] Percentages indicate portion of total effort.

FIGURE 1
FUNDING OF PROJECTS BY KING-MUIR CATEGORY

whole animal effects (e.g., behavioral effects in primates and somatic mutations in mice).

Objectives of these research projects include determination of the effects of airborne respirable particulates on the phagocytic activity of rabbit alveolar macrophages and investigation of hormonal regulation of the effects of chemical carcinogens on endometrial cells.

Different agents or pollutants associated with various energy technologies are being subjected to biological screening and testing systems. These include crude effluents from alternate energy sources, coal conversion by-products, emission condensates, fractions and subfractions of complex mixtures from energy-related technologies (e.g., Synthoil, Synthane), airborne respirable particles and gases, fibrous minerals associated with the extraction of ores, trace elements (e.g., thallium), and particulates (e.g., metal-coated fly ash particles from coal combustion, fluidized bed combustion, and coal gasification). Some of the projects involve separation, classification, and characterization of the samples prior to testing. Emissions from combustion of eastern and western coals are being characterized, and their toxicologic effects are being compared.

Research projects pertaining to King-Muir Objective #1 were funded at approximately $8.5 million through fiscal year 1978, or about 15 percent of the total expenditures for the Health Effects

Research Program. Allocations for individual research projects in this category ranged from $64,000 to $530,000.

4.2 DOSE AND DAMAGE INDICATORS

King-Muir Objective #2, Dose and Damage Indicators, entails the development of the techniques needed for evaluation of the consequences of human exposure to energy-related toxic substances. The research projects in this category are concerned with improving analytical indicators of exposure, developing techniques for estimating damage, or developing more rapid and more sensitive techniques for determining adverse biological activity. Biological activity can be determined by examining subtle metabolic and biochemical changes in cells, tissues, or whole animals.

In some cellular studies, rabbit alveolar macrophage cells are being used to examine the toxic properties of trace metals and particulate material. Response indices include cell viability, ATP content, functional integrity, and various metabolic enzyme changes.

Heavy metals (e.g., lead and cadmium) are applied to cell cultures derived from nerve, liver, muscle, and lung tissue. The effects of metals on general growth, DNA and protein synthesis, metabolism, and expression of differentiated functions such as reproduction are being examined in cells from various animal species. Some metals seem to interfere with the synthesis of important macromolecules like collagen, a component of the connective tissue. The lack of proper synthesis of collagen could explain the damage some metals cause to tissue structure. The ability to measure biochemical changes such as the level of collagen synthesis in the human body may aid in quantifying the levels of specific metal pollutants to which the person had been exposed and the subsequent damage.

Bioindicators of exposure to sulfur and nitrogen oxides, ozone and hydrocarbons are being sought. Selected mammalian cell lines (e.g., Chinese hamster ovary, Syrian hamster embryo, and mammalian lymphoid cells) as well as human fibroblast and lymphocyte cells are used to detect mutation and other biological changes. Some of the changes being examined as possible bioindicators include synthesis and repair of DNA, alterations related to mutagenesis, carcinogenesis and teratogenesis, and reproductive effects. Newly developed bioindicators will aid in determining the genotoxic nature of energy-related pollutants.

A variety of epithelial cell lines from various animal species are being tested to determine the neoplastic transformation potential of specific pollutants. Because most human tumors are derived from epithelial tissues, epithelial cell lines are highly relevant as biological screening tools.

A number of new cell lines that possess particular sensitivity for certain types of agents are being developed for use in mutagenesis screening. The new cell lines will be used as cellular models.

They should provide estimates of exposure and the relative toxicities of a variety of agents.

The toxicity of energy-related compounds to spermatogonia and other germ cells is being investigated in mice. Mutations in sperm cells of mouse and man that are caused by toxic agents constitute an important indicator of human susceptibility. New computerized scanning procedures are being developed to detect aberrant sperm cells. These new procedures should improve the accuracy in detecting aberrant cells and should decrease the counting time so that more test samples can be examined.

Techniques are being developed for examining behavioral changes in rats and monkeys following exposure to sulfur dioxide, sulfuric acid, auto exhaust particulates, and coal conversion pollutants. Behavioral changes could become important new indicators of the consequences of exposure to pollutants. However, the ability to estimate damage and toxicity from behavioral changes is very limited at present.

Research projects for King-Muir Objective #2 received approximately 7.6 million dollars in funding through fiscal year 1978. This sum amounts to 13 percent of the total expenditures for the Health Effects Research Program. Allocations for individual projects ranged from $25,000 to $730,000.

4.3 METABOLISM OF HAZARDOUS AGENTS

In the research projects funded under King-Muir Objective #3, Metabolism of Hazardous Agents, the metabolism of energy-related toxic substances is being studied. The mechanisms and kinetics of uptake, distribution, and excretion of toxic agents are being examined as well as the relationship between metabolism and toxicity. Knowledge of the mechanisms for metabolizing and detoxifying toxic pollutants is probably the single most important piece of information necessary for an understanding of the toxicity of substances.

Methods are being developed to determine the concentrations of toxic agents and their metabolites in various body tissues and organs. The uptake and accumulation of lead in brain tissue is being investigated to determine the effect of lead on calcium transport at the blood brain barrier. The mechanisms of toxicity and detoxification of heavy metals such as lead are being determined. The effect of heavy metals on the detoxification of sulfide by sulfide oxidase in tissues is under investigation. New techniques being developed for determining the concentrations of toxic substances in tissues and body fluids include innovative uses of radioactively labeled compounds and new spectrographic procedures.

Much of the research effort on the toxicology of energy-related agents focuses on the pulmonary system because most pollutants will enter the body through the lungs. New techniques are being used to examine the physical and deposition characteristics of pollutants such as fly ash in the lung. These characteristics are then associated with morphological changes and damage in the lungs. Topics of investigation include the biochemical mechanisms of toxicity for pollutants such as sulfur and nitrogen oxides. The effects of pollutants on the uptake of antioxidants (e.g., vitamin E) and on blood and liver enzymes are also under study. The effect of toxic agents on the alveolar macrophage metabolism of carcinogens is being correlated with lung cancer induction. Various biochemical mechanisms that relate lung disease to chemical exposure are being investigated.

Mathematical, physical, and animal models are being developed to predict the levels and rates of deposition of particulates in various regions of the lung. These models will be used to correlate the deposition of particulates in specific regions of the lung with the sites at which cancer and other diseases are initiated. Compartmental models are also being developed for use in predicting total body burdens of various energy-related pollutants.

Approximately $6.4 million was obligated through fiscal year 1978 to the research projects funded under King-Muir Objective #3. This funding constitutes 11 percent of the total expenditures for the Health Effects Research Program. Funding for individual projects in this category ranged from $20,000 to $610,000.

4.4 EVALUATION OF HAZARDS TO MAN

Research projects funded under King-Muir Objective #4, Evaluation of Hazards to Man, are concerned with the development of techniques for correlating animal study findings with human diseases. Epidemiological and clinical studies of selected human populations are used to determine the frequency of various disease states in man. These studies may also indicate the potential causes of some of the diseases, even though their etiology is not clear and the mechanisms of disease production are unknown. Selected cellular and animal models can assist in determining the mechanisms and etiology of disease and, finally, acceptable human exposure levels.

The effects of energy-related agents on human respiratory function are receiving considerable attention. The effects on the lung of acid sulfates, sulfates, nitrogen dioxide, nitric acid, nitrates, ozone, carbon monoxide, hydrogen sulfide and various carcinogens such as 1,2-benzanthracene are being determined. The deposition of these agents in the lung and their metobolism are being examined. Clearance, defense, damage, and repair mechanisms in the lung are being studied. The interaction of two or more agents is being investigated; for example, the interactions of diesel exhaust and coal dust are being examined in laboratory animals.

The effects of pollutants on other organs are also under study. These studies include the effects of nitrogen dioxide and ozone on cardiac, pulmonary and peripheral circulatory function in adult men who are experiencing heat stress at various activity levels. The long-term effects of acute and chronic exposures to pollutants and radiation on the development of the rat brain and nervous systems are being studied in a project that examines rat offspring for a number of generations. Prenatal exposure to microwaves, electric fields, and metallic pollutants is being used to determine the effects of such exposures on the developing nervous system and the development of latent behavioral changes. The neurochemical effects of these exposures are also being examined.

The genetic effects of energy-related agents are being investigated, and selective teratogenic test systems are being developed. Mutagenic, carcinogenic, and reproductive effects are being studied in laboratory animals and cellular test models. Species-to-species carcinogenesis extrapolation techniques are being developed for the comparison of data on various animals and man. Risk assessment methods involving more complex factors are being developed. The development of statistical methodology using computer techniques for low dose extrapolation from the high doses used in laboratory testing should provide better correlation among cellular models, animal models, and man.

Epidemiological studies of the effects of pollutants on selected human populations are in progress. Occupational exposures to acid sulfates, sulfur dioxide, sulfates, nitric acid, nitrogen dioxide and nitrates are being studied. Epidemiological studies can be made of people living near fossil fuel-fired power plants. With continuous air quality monitoring, the deterioration in air quality that is caused by these plants can be determined and correlated with the health effects data. People are being examined for adverse health effects attributable to water supplies that originate in coal extraction areas. Workers in the shale oil, coal gasification, coal liquefaction, mineral wool fiber, and insulation industries are being studied for occupational diseases.

A chemical repository for alternate source materials and a national environmental specimen bank are being organized. Establishment of these repositories necessitates development of sampling, storage, chemical analysis, and standardization methods.

The sum of approximately $30.3 million constitutes the Interagency funding through fiscal year 1978 for the research projects designed to meet King-Muir Objective #4. This level of funding amounts to 52 percent of the total expenditures for the Health Effects Research Program. Allocations for individual research projects in this category ranged from $8000 to about $1.6 million.

4.5 DAMAGE, REPAIR, AND RECOVERY PROCESSES

King-Muir Objective #5--Damage, Repair, and Recovery Processes--concerns the determination of these processes in biological systems that are exposed to hazardous agents associated with energy technologies. Many research projects in this category involve establishing quantitative methodologies that relate mechanisms of toxicity to agent exposure. Cell models used in studying the damage, repair, and recovery mechanisms include blood platelets; cultured nerve, heart muscle, and endometrial cells; and lung fibroblasts and macrophages.

Methods of evaluation include examining the changes that occur in the viability, morphology, plasma and organelle membrane characteristics, locomotion, and biochemical constituents of the cells.

The cellular regulatory processes involved in the metabolism of polycyclic aromatic hydrocarbons (PAH) are under study. The role of free radical intermediates formed during PAH metabolism is being investigated by electron spin resonance spectroscopy. _In vivo_ DNA repair assays are being conducted in mice; the germ cells are examined to determine the ability of PAH to induce unscheduled DNA synthesis. In addition, the mechanism by which light (ultraviolet and visible) synergizes the tumorigenicity of PAH on skin is being investigated.

The effects of metals (e.g., selenium, beryllium, and iron) on regulatory processes in damaged cells, specifically their ability to inhibit induction by hormonal regulators, are being studied. The interaction of heavy metal ions found in the effluents from oil shale processing (e.g., copper and cobalt) with human plasma and tissue proteins is being investigated. The uptake of cadmium by pulmonary alveolar macrophages, the intracellular distribution of cadmium, and alterations in macrophage function caused by cadmium are being studied in rabbits.

Research is being conducted on the effects of atmospheric pollutants (e.g., sulfur and nitrogen dioxides) on alveolar macrophages. Studies in progress are attempting to demonstrate that the toxicities of ozone and nitrogen dioxide are related to the ability of these compounds to initiate peroxidation of unsaturated fatty acids; and that vitamin E as an antioxidant can minimize lung damage. The role of vitamin A in cell cycle kinetics of the hamster respiratory tract resulting from exposure to nitrogen dioxide is being investigated; dietary vitamin A appears to be an important nutritional factor in the repair of nitrogen-dioxide-gas-induced injury of the respiratory tract.

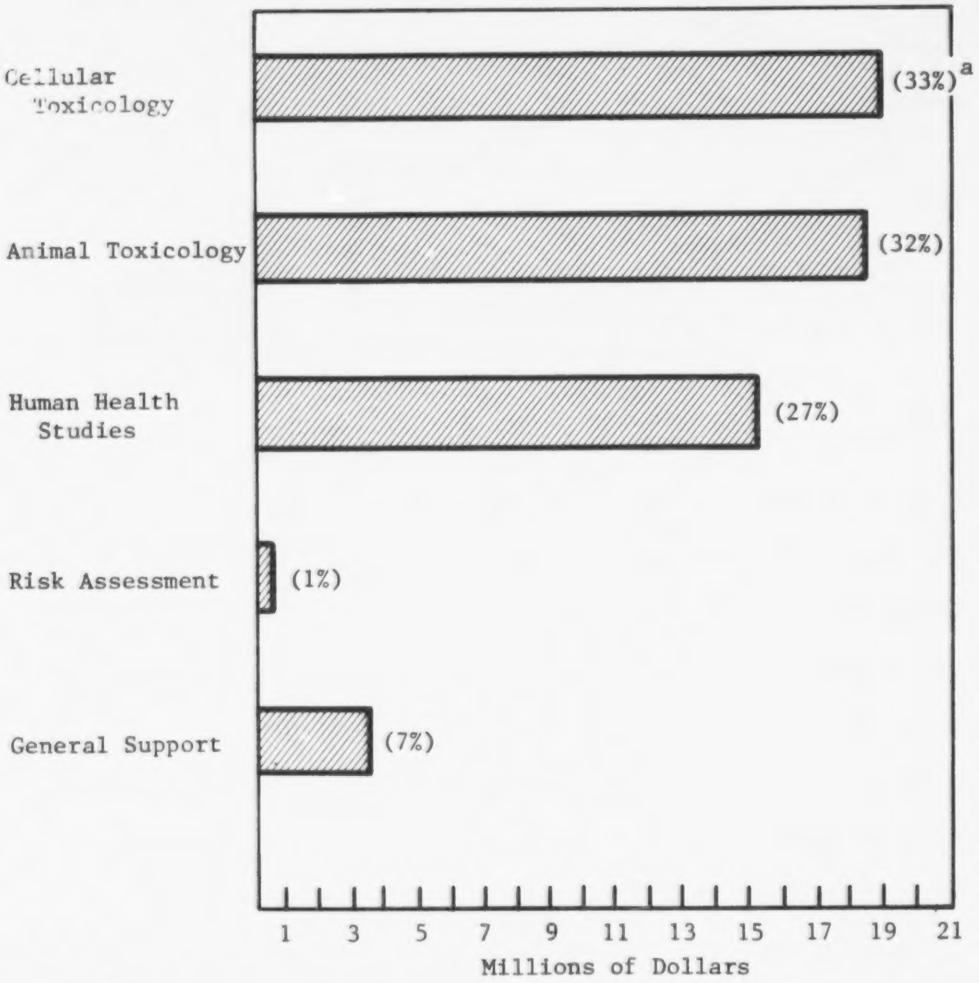
Research projects funded under King-Muir Objective #5 received approximately $5.6 million through fiscal year 1978. This allocation represents 9.5 percent of the total expenditures for the Health Effects Research Program. Funding for individual research projects in this category ranged from about $9000 to $920,000.

SECTION 5

PROGRAM REVIEW FROM THE PERSPECTIVE OF SCIENTIFIC DISCIPLINES

In this section, the Health Effects Research Program in the Federal Interagency Energy/Environment R&D Program is reviewed from the perspective of the scientific discipline of research emphasis. For the purpose of this review, the following scientific discipline categories were selected: Cellular Toxicology, Animal Toxicology, Human Health Studies, Risk Assessment, and General Support. The funding through fiscal year 1978 in each scientific discipline category is indicated in Figure 2.

The Health Effects Research Program component of the Federal Interagency Energy/Environment R&D Program is designed to examine the potential for adverse impacts on human health of energy-related agents and pollutants. The cellular toxicology discipline involves the use of cell and tissue cultures as screening models for the evaluation of the potential toxicity of various pollutants. When adverse effects are observed in cellular systems, more complex tissue, organ, and whole animal systems can be used to determine more definitively the types of toxic effects that might occur in humans.



[a] Percentages indicate portion of total effort.

FIGURE 2
FUNDING OF PROJECTS BY SCIENTIFIC DISCIPLINE CATEGORY

Human health studies are a pivotal part of the program. The data obtained from environmental, occupational, and experimental exposures of humans to energy-related pollutants and agents are compared with data from the cellular and animal toxicology studies. From these comparisons, the risks to human health from exposure to various energy-related agents can be asessed.

5.1 CELLULAR TOXICOLOGY

The Cellular Toxicology discipline involves the development and use of cell and tissue cultures as screening tools for the evaluation of potentially toxic agents. Toxicity and damage indicators are monitored in various cultures to evaluate the biological effects of specific types of toxic agents on cellular structure and function. The ability of a damaged cell to repair itself and metabolize and detoxify an invading agent is essential to the cell's continued survival and its ability to deal with the insult of a toxic agent. For these reasons, the damage and repair mechanisms in cells are under study, and the metabolism of toxic agents in cellular systems is being investigated.

Research in the Cellular Toxicology discipline is of five major types: Biological Screening, Development of Screening Methods, Toxicity and Damage Indicators, Damage and Repair Mechanisms, and Metabolism Studies. Cellular methods alone cannot definitively assess the effects that toxic agents will have on man; however, they do provide an indication of potential toxicity and help determine the relative toxicities of various energy-related agents. The cellular toxicology discipline, therefore, complements the animal toxicology efforts and the human health studies.

Funding for research in the Cellular Toxicology discipline was about $19.1 million through fiscal year 1978. This sum represents 33 percent of total expenditures for the Health Effects Research Program. Funding for individual research projects in this category ranged from $20,000 to $1.5 million during this period.

5.1.1 Biological Screening

The research projects that pertain to biological screening are designed to provide qualitative and semiquantitative information on the adverse health impacts of energy-related activities. In the bioscreening program, cell and tissue cultures are used as rapid, accurate, and inexpensive biological assay systems to examine large numbers of energy-related materials in order to identify potentially toxic agents and to estimate relative toxicities. Crude complex pollutant mixtures, isolated fractions, and purified substances are screened. The crude mixtures are identified chemically and physically before testing, although the components are not necessarily separated and purified.

The bioscreening program uses several response indices to assess the biological activity of a particular substance--the substance's carcinogenic, mutagenic, teratogenic, and toxic properties, and its effects on reproduction. The biological activity of a substance is sometimes implied indirectly (e.g., mutagenic screening is used to identify potential carcinogenicity).

A variety of energy-related air pollutants is being tested for carcinogenic potential using the CH3/10T 1/2 and BALB/c 3T3 neoplastic transformation bioassays. The sensitivity of the assay systems is improved by the introduction of metabolic activation preparations to activate materials being tested. Morphological transformations and biochemical changes are being monitored as indicators of neoplastic cellular changes. The neoplastic transformation potential of specific agents on epithelial cell lines of hamsters, rats and mice is being determined. Since most human tumors are derived from epithelial tissues, these cell lines are highly relevant as screening tools.

Agents obtained from coal and oil shale processes are being screened for their ability to enhance carcinogenesis (i.e., as co-carcinogens) and to induce other adverse biological activity. The use of rodent cell lines in bioassay systems provided indications that induction of some DNA lesions occurs differently in rodent and human cell lines. These findings demonstrate the need for caution in extrapolating research results from animal to human cell lines.

Agents from low-BTU industrial gasifiers and coal liquefaction operations are being examined to determine their potential for inducing DNA lesions or changes such as chromosome breaks, chromatid exchanges and nondisjunctions in DNA repair synthesis in polymorphonuclear leukocytes (PMN).

The mutagenic potential of numerous energy-related pollutants is being determined using several microbial test systems (e.g., *Salmonella typhimurium* histidine-deficient strains). Because the mutagenic agents are in many cases the metabolites of the test agents rather than the test agents themselves, metabolic activation preparations are added to the test systems along with the agent that is being tested. Structure-activity relationships are being sought and have been demonstrated for some chemical categories of pollutants.

Selected mammalian cell lines (e.g., Chinese hamster ovary [CHO], Syrian hamster embryo [SHE], and mammalian lymphoid cells) are being used to detect point mutations that are caused by exposure to selected energy-related pollutants. Mutagenic screening involving multiple loci tests uses electrophoretic methods to determine loci changes. The multiple loci systems are used to test crude and fractionated hydrocarbon samples and heavy metals generated in coal conversion and oil shale processes.

Some cellular toxicity screening studies use rabbit alveolar macrophages (RAM) for testing the effects of metallic-oxide-coated and uncoated fly ash and selected metal ions. The response indices used in these studies include cell viability, ATP content, functional integrity, and various enzyme activities.

5.1.2 Development of Screening Methods

A number of research projects in the Cellular Toxicology discipline were designed for the development of screening methods. Screening methods are needed that will provide accurate and reliable data for estimating the hazards of toxic agents. Many techniques that are used at present require standardization and additional development. New screening methods are needed to investigate a wide variety of biological indicators and to screen specific classes of agents that cannot be screened by methods now available. There are many new types of crude mixtures and individual substances that must be screened for biological activity, and current screening methods will need modification before they can be used effectively with many of these substances. Furthermore, the practical application of cellular screening methods necessitates the development of new equipment and instrumentation.

Microbial screening systems that are under development (e.g., *Escherichia coli* K12 and Coliphage T4) will introduce new types of biological response indicators in addition to those found in the present testing systems. The microbial screening systems now in use (e.g., *Salmonella typhimurium* and *Saccharomyces cerevisiae*) are being modified to screen selected air pollutants as either complex mixtures or individual components. Multiple-marker assays are being developed to measure the frequency of induced forward mutation. Some systems are being modified to test human urine for carcinogenic metabolites that may have originated from alternative energy sources. Various synthetic fuel oil samples are being screened in specially modified microbial systems.

Screening methods that use mammalian somatic cell lines (e.g., CHO, SHE, mouse embryo [C34/10T 1/2], and V-79CH lung cells) are being developed. Neoplastic transformation response is being determined by identifying morphological, biochemical, and growth changes that occur after the cells are exposed to carcinogenic agents. Improved methods are being developed for determining cell transformations; these include detection of cytochemical markers by microfluorometry, and flow system analysis. Improved methods of sorting normal and transformed cells will increase the number of cells that can be handled and will improve sorting accuracy. Multiple site screening methods for mutations are being developed for use with somatic cells when electrophoretic shifts are examined.

Rabbit alveolar macrophage cells are being examined as sensitive indicators of the toxic effects of airborne particulate materials. It was found that ATP content is an especially sensitive indicator of phagocytosis and particle toxicity. Selected air pollutants are being examined for genotoxic effects using cultured liver cells (hepatocytes) from mice.

Epithelial cell lines are being developed for screening purposes. Cultured human lymphocytes and hamster lymphocytes are being used in modified host-mediated assay systems and a variety of other mutagenesis testing systems. Alterations in metabolic, enzymatic, and growth properties, rates of chromosome exchange, and other characteristics are being determined. The effects of chemical exposure on the cellular immune system of hamster lymphocytes are under study. Quantification of immune system inhibition by toxic agents would be an important screening tool. Enzyme profile changes in mouse embryo and human lung fibroblasts caused by exposure to toxic agents are being determined. Flow cytometry can now discriminate between normal and transformed human lung fibroblasts.

5.1.3 Toxicity and Damage Indicators

In the Cellular Toxicology research projects that pertain to toxicity and damage indicators, the respiratory tract and skin receive major consideration because these are generally the principal routes by which man is exposed to energy-related pollutants. Indicators of respiratory tract damage focus on the alveolar macrophage because it represents the primary means of defense against inhaled materials and on the lung epithelium because of its rapid mitotic rate and proclivity to develop cancer.

Developments in the macrophage system include the addition of enzymatic, morphological, and functional indices of damage to the existing cell viability measurements. The ability to monitor the functional integrity of the alveolar macrophage is important because of its involvement in lung clearance mechanisms.

Much effort is being expended to determine the mechanisms involved in damage and preneoplastic changes after chemical insult. Studies use various epithelial lesions to determine potential markers for preneoplasia. Lung epithelial cells demonstrate increased cell turnover in response to irritation, and studies are now underway to determine whether the turnover rate can be used as an indication of early damage and progression to latent disease including cancer.

The biochemical mechanisms of pulmonary injury and the biochemical response to energy-related pollutants are being investigated. The effect of agents on antiviral mechanisms are being correlated with the general immunological competence of lung cells so that decreases in cell viability can be correlated with chemical insult as indicators of potential damage.

Research is being done on the mechanisms involved in skin tumor induction by chemical carcinogens. Skin and liver cell cultures are used in attempts to detect cytological and biochemical changes that correlate in time with the promotion and progression of cancer.

At the molecular level, molecular damage to DNA and various proteins caused by metals, metal ions, and organic compounds associated with fuel and energy production is being investigated. For example, it was found that lead and mercury inhibit DNA synthesis and induce base error in DNA. The mechanisms involved in mutations are being determined. The control of frame shift mutation can be achieved by using a competitive agent that competes for the same site as the agent that causes mutation. Emphasis is being placed on the DNA damage that results from simultaneous exposure to chemicals and physical agents.

5.1.4 Damage and Repair Mechanisms

Another aspect of the Cellular Toxicology discipline category is the study of damage and repair mechanisms. Substantial effort is being directed toward evaluating the basic mechanisms of pollutant interaction at the cellular and subcellular levels. At the molecular level, the mechanisms of damage may transcend mammalian species differences and thereby aid in extrapolating information from experimental animals to man. Recent studies with carcinogenic polynuclear hydrocarbons indicate that exposure to these chemicals in the activated state results in DNA binding according to first order kinetics. Similar kinetics have been demonstrated for gene mutations and the initiation phase of carcinogenesis caused by several of the same hydrocarbons. Studies are being made of the mechanisms involved in DNA damage and repair in various germ cell stages of mammals. Excision repair and unscheduled DNA synthesis are two repair mechanisms that are receiving considerable attention.

Pulmonary epithelial cell biology is being examined in order to attain a more thorough understanding of repair, replication, and other mechanisms. The effect of toxic agents on the enzyme synthesis necessary for cell recovery after damage is being studied. All regulatory processes in damaged cells are important to the cell's ability to recover from chemical insult and to remain viable. The interactions between damage and repair mechanisms also provide a better understanding of neoplastic cell transformations.

Because of their sensitivity and proliferative activity, stem cells tend to magnify injuries. Consequently, the immune and hematopoietic systems, both of which contain stem cells, have been suggested as good indices of pollutant toxicity. Humoral and cell-mediated immunity are being examined in rabbits exposed to polynuclear hydrocarbons that were derived from coal gasification and oil shale processes.

Although some progress has been made in studies of repair in prokaryotic organisms, there is a need for more work with mammalian cells, especially human cells. Such work is just beginning and is hampered by the lack of repair-deficient mutants, except for cells obtained from people with xeroderma pigmentosum. Efforts are underway to develop such mutants.

5.1.5 Metabolism Studies

The last subcategory of research projects in the Cellular Toxicology discipline consists of metabolism studies. The biochemical and metabolic functions of a cell are basic in determining the effects that toxic agents will have on cellular integrity. The metabolic alterations of energy-related substances can lead to either detoxification or increased toxicity. Many substances are not in themselves carcinogenic although their metabolites can be carcinogenic. The carcinogenic potential of a pollutant may very well depend on the ability of the exposed organism to metabolize the pollutant into a carcinogenic metabolite(s). An understanding of the biochemical changes that occur in cells following insult by a toxic substance is critical to understanding neoplastic changes in cells, tumorigenesis in organs and tissues, and other pathological changes.

Biochemical changes that occur in the lung are receiving considerable attention because of the importance of the lung in pollutant exposure. The reactions of atmospheric contaminants with receptors in lung tissue are being studied. The effects of pollutants on pulmonary function are being determined. Of particular interest are the molecular interactions of pollutants (e.g., organometallic compounds) with membrane constituents and the subsequent effects on membrane properties. Free radical formation during lung metabolism that leads to superoxide formation and auto-oxidation of lipids and lung surfactants is being studied. The interactions of metal ions such as cadmium with pulmonary alveolar macrophages are under study. It was determined that serum proteins play an important role in the uptake and binding of cadmium by macrophages.

Toxic agent metabolism in cultured cells is being correlated with metabolism in animals so that more metabolically effective cell lines can be used in screening systems. Some cellular screening systems totally lack the ability to metabolize pollutants and, therefore, metabolic activation preparations must be added to the cellular systems. The improvement of metabolic activation preparations for cellular testing is vitally important to the success and worth of the systems in predicting adverse human health effects.

5.2 ANIMAL TOXICOLOGY

Animal toxicologic studies use animal test systems for screening pollutants for possible toxic effects and for estimating dose-response relationships. Animal studies are short term (e.g., screening tests and acute exposure studies) or mid-to-long term (e.g., metabolism, chronic exposure, and carcinogenesis studies). Some chronic exposure studies last the lifetime of the laboratory animal. Animal studies provide important information for assessing the potential short- and long-term hazards to man of energy-related substances.

Although a major disadvantage of whole animal testing is the difficulty in extrapolating findings from animals to man, those tests provide many advantages over human health studies. Ethical considerations restrict the testing of hazardous substances in people. Animal tests are quicker and less expensive than human toxicologic studies. Human subjects are highly variable and are difficult to control under test protocols, whereas animal environments and experimental conditions can be tightly controlled and test protocols judiciously followed in experimental studies. Specific animal species with unique characteristics are used to provide particular types of information for predicting human effects. New strains of laboratory animals have been developed for examining specific types of toxic actions or specific classes of substances. Metabolism studies in whole animals provide important clues as to why certain substances react as they do in man to produce toxic effects and diseases.

Research projects in the Animal Toxicology discipline category were divided into five groups: Toxicologic Testing and Screening, Development of Testing and Screening Methods, Toxicity and Damage Indicators, Damage and Repair Mechanisms, and Metabolism Studies. Review of this scientific discipline is presented below in terms of these five subcategories.

Funding through fiscal year 1978 for the research projects in the animal toxicology discipline category amounted to approximately $18.8 million. This sum constitutes about 32 percent of the total funding for the Health Effects Research Program. Individual research projects in this category received allocations that ranged from $29,000 to $921,000.

5.2.1 Toxicologic Testing and Screening

Some of the research projects in the Animal Toxicology category involve toxicologic testing and screening using whole animals. In most of these studies, pollutant exposure is by inhalation.

The inhalation studies include detailed studies of the structural, biochemical, and functional changes in the lung that result from pollutant exposures. Pollutants under consideration include sulfur-containing compounds, nitrogen oxides, oxidants, metals, and selected hydrocarbons.

Biochemical indicators of damage and adverse effects in animal systems are being used as endpoints in the screening protocols. The various laboratory methods used to monitor these indicators include flow system analysis, cell separation, spin-labeling, spectroscopic, and mass balance techniques. Tissue samples are examined for physiological, structural, biochemical, and immunological changes. Early deviations in one or more of these or other factors can be used as indicators of toxicity. Many of these indicators can be related directly to the development of damage and disease caused by toxic agents.

A series of studies on the effects of synfuels and specific coal conversion products on the mouse reproductive system are underway to identify chemically induced chromosomal aberrations in germ cells and to detect cell death in mouse oocytes. The tests used include dominant lethal and heritable translocation tests. The mouse specific-locus method is used to quantify chemically induced gene mutations that are caused by exposure to energy-related substances.

The neurotoxicity and potential for behavioral modification in monkeys of sulfur-containing compounds, hexabrominated biphenyls, and other hydrocarbon pollutants are being determined. The behavioral effects of radiation from microwaves, electrical fields, and tritiated water are being studied in monkeys, rats, and other laboratory animals. In addition to nervous system effects, the effects on reproduction, organ function and structure, and biochemistry are being monitored.

Fruit flies (Drosophila) and fish (Poecilia formosa) are used in nonmammalian animal screening systems. Drosophila are used to screen a number of environmental pollutants for genotoxicity which is manifested, for example, by chromosomal aberrations that can block inheritance of specific traits by offspring flies. Fish are used for quantitative evaluation of the carcinogenicity of coal conversion products.

5.2.2 Development of Testing and Screening Methods

The development of testing and screening methods is an important subcategory of the Animal Toxicology scientific discipline. New tests and screening methods are needed that can be performed quickly and relatively inexpensively using laboratory animals. The variations in response induced in different animal species by the same pollutant is a complexity of animal testing that requires further investigation. Application of the findings from whole animal testing to the estimation of human risk from toxic agents has many uncertainties that need clarification. Proper modification of animal testing protocols following the development of new methods will increase the usefulness of animal test data in predicting human risk from energy-related agents.

Much of the emphasis in developing new techniques and testing systems centers on the lungs. Indicators of biochemical and immunological changes in various types of lung cells after animals are exposed to sulfur and nitrogen dioxide and specific hydrocarbons are being investigated. Dose-response curves based on the exposure levels to specific agents and the resultant biochemical changes could contribute much to the understanding of pulmonary toxicity that results from pollutant inhalation. Methods using tracheal transplants and grafts for examining neoplastic cell transformations are being developed: the trachea is removed from a rat or hamster, pellets containing toxic substances are placed in the trachea which is transplanted into another animal of the same species, and changes in the transplanted tracheal epithelium are then monitored. New methods are being developed to produce aerosols from substances such as fly ash so that more effective inhalation studies can be performed with particulate pollutants.

Another area receiving considerable attention is neurotoxicity and behavioral changes that are induced by toxic agents. Automated computer pattern recognition systems using closed-circuit television are being developed for use in the study of primate behavior. After baseline data on normal primate behavior are compiled, monkeys will be exposed to pollutants and the "seeing computer" will be used to monitor changes in pattern recognition, spontaneous behavior, learning and memory abilities, and stimulus response. Monkeys will be exposed to thallium, methyl mercury, and hydrocarbons from coal conversion and synfuel production.

New strains of mice that have marked chromosomal inversions are being developed for use in studying the effects of chemically induced point mutations on the offspring of exposed animals. The development of electrophoretic methods to detect enzyme variants in new mouse strains should maximize the sensitivity of the point mutation assay. The effects of point mutations on offspring are being investigated in a number of animal species (e.g., dogs, rats, and mice). An understanding of the mutagenic effects on offspring of known mutagens will help in the development of new screening methods.

Reproductive studies are examining the effects of pollutants on mouse oocyte death and sperm morphology. Sperm shape variation as an indication of sperm damage is being investigated in hamsters, rabbits, and other animals including man. These studies should lead to faster, more efficient, and less costly methods of determining the reproductive effects of energy-related agents.

5.2.3 Toxicity and Damage Indicators

Much of the effort in the research projects that pertain to toxicity and damage indicators is directed toward investigation of indicators of lung disease. Many energy-related pollutants cause lung damage that can lead to lung disease. Early indicators of potential damage are being detected in current studies; these might help to avoid the damage resulting from pollutant exposures that could lead eventually to lung disease in man.

The early indicators of damage resulting from the inhalation of sulfur acids, nitric acids in aerosols, and particulates that contain metals (e.g., cadmium) and oxides of metals (e.g., lead, mercury, and cadmium) are being determined. Alveolar and bronchial clearance mechanisms are being studied to determine their ability to protect the lung against foreign agents. Biochemical, morphological, and physiological indicators of lung damage are being correlated with agent exposure.

Of special importance are the lung's defense mechanisms against infectious invasion. The effects of coal gasification products on the pulmonary defense mechanisms are being determined. Pulmonary bactericidal responses, cell population changes, and the role of alveolar macrophages in the lung defense mechanisms are being examined. Substances that might offer protection against damage from exposure to toxic agents are being studied. The interactions of known pulmonary carcinogens with lung-irritating pollutants are being determined in inhalation studies with pollutant and carcinogen mixtures. These studies should lead to better understanding of the early mechanisms that are involved in the induction of lung disease by toxic agents.

The effects of sulfur dioxide and carbon monoxide-sulfur dioxide mixtures on the development of the conceptus during gestation are being determined in mice and rabbits. The offspring are examined for external and internal alterations just before birth. Factors that affect the cross-placental transfer and teratogenicity of various metallic pollutants are being sought. For example, the kinetics of lead distribution are being studied. The effects of cadmium on the ultrastructure of mouse spermatogonia are being determined as well as the effects of environmental pollutants on specific reproductive tract functions.

5.2.4 Damage and Repair Mechanisms

Another aspect of the Animal Toxicology discipline is the study of damage and repair mechanisms. Of particular concern are the damage and repair mechanisms of the lung because most animal testing entails inhalation studies. Once the lung is injured, its ability to repair itself is of considerable importance if the lung is to remain viable. If, for some reason, the lung is not able to repair itself properly and to a sufficient extent, then pulmonary disease is likely to develop. For this reason, the mechanisms involved in lung repair are being investigated.

Laboratory animals are exposed to specific pollutants that cause different degrees of lung damage and the immune and repair systems are then examined. The effectiveness of substances such as vitamin E in preventing oxidative damage and the effects of vitamin A on cell cycle kinetics are being determined. For example, vitamin A deprivation in animals causes a lack of cell reproduction so that damaged cells are not replaced and the necessary adaption of the lung to air pollution does not proceed correctly.

The immune system is also monitored during the development of respiratory carcinogenesis. Studies of toxic trace metals require the development of new methods of tissue analysis. Therapeutic procedures are being developed that can be used to reduce metal concentrations in tissues effectively.

5.2.5 Metabolism Studies

An understanding of the metabolism of toxic agents in animals will help explain the deleterious effects that many pollutants have in man. With many pollutants, it is not the substance itself but rather its metabolites that are toxic. If the formation of toxic metabolites can be prevented and/or if levels of toxic agents in the tissues can be effectively reduced, the deleterious effects of many pollutants could be prevented. Metabolism studies involve measuring concentrations of pollutants in animal/human tissues and fluids and determining uptake, distribution, excretion, and the various metabolic pathways of energy-related agents in laboratory animals and man. Once these metabolic data are obtained, the toxic action of pollutants can be better understood and possibly prevented.

Methods are being developed to use gas chromatographic-mass spectrographic systems to determine the levels of specific energy-related substances in human tissue, blood, and various body fluid samples from adults and children. The metabolism of inhaled trace metal emissions from combustion processes is being investigated. Levels of trace metals in biological fluids, vital organs, and bone are being determined. The metabolism and mode of action of nitrogen dioxide and hydrocarbon solvents in the lung are being studied. Lead metabolism in the immature brain of young rats is being investigated in order to better understand the mechanisms involved in lead toxicity to the brain. The effects of competing agents on the metabolism of the host animals are being determined; for example, the effects of endogenous antioxidants on the metabolism and toxicity of nitrogen dioxide in the lung are being studied in hamsters. Pollutant-caused immunological changes that might hinder defense mechanisms against chemical insult are receiving considerable attention.

Using metabolic data, pharmacokinetic models are being developed that will predict distribution, tissue concentrations, and excretion rates of specific pollutants. Special emphasis is being placed on species sensitivity to the bioaccumulation of energy-related compounds such as polychlorinated biphenyls (PCBs).

5.3 HUMAN HEALTH STUDIES

The research projects pertaining to Human Health Studies were grouped in four subcategories--Epidemiological Studies, Clinical Studies, Toxicologic Studies, and Support/Other--for the purposes of this program review.

The Human Health Studies discipline category received approximately $15.3 million in funding through fiscal year 1978, about 27 percent of the total expenditures for the Health Effects Research Program. Allocations during this period to individual research projects in this category ranged from $8000 to about $1.6 million.

5.3.1 Epidemiological Studies

Research involving epidemiological studies includes investigation of the occurrence and effects of occupational exposure to various agents, the morbidity/mortality that results from energy-related work environments, and the industrial hygiene practices at various energy-related facilities. Research projects include such diverse studies as determining the adverse health effects caused by drinking water contaminated with by-products of energy production, and assessing the effects of inhaling insulation material substances.

With regard to the energy-related work environment, health effects studies are being conducted on workers in oil shale, coal gasification and liquefaction, solar energy, coal-fired power, coal-cleaning, and petroleum product facilities. In other occupational health studies, miners and deep-sea divers are being examined. For example, as part of the oil shale worker study, oil shale workers at the Anvil Points facility were identified, death certificates of former employees were reviewed, and oil shale workers and control subjects were given medical examinations.

Pollutant-specific research is being conducted on workers exposed to sufuric acid, sulfur dioxide, sulfates, nitric acid, nitrogen dioxide, nitrates, ozone, and insulation materials (e.g., clay, small glass, and mineral wool fibers). In one study, 300 salt miners who worked in five mines, all of whom had been exposed to nitrogen-containing gases from diesel fumes, were examined by chest X-rays and pulmonary function tests and were surveyed by questionnaires on respiratory dysfunction. In addition, research is being conducted to detect chromosomal abnormalties in the peripheral blood lymphocytes of welder trainees who are occupationally exposed to ozone.

Other studies involve determining acute and chronic oral toxicities from exposure to coal gasification emissions and emission fractions. The levels of toxic elements in various organs of the workers in coal gasification plants are being measured. Human teeth are being analyzed by atomic absorption spectrophotometry to determine the exposure histories of people who live near energy-related facilities.

5.3.2 Clinical Studies

Clinical human health studies usually involve the direct observation of patients in clinical situations. Other research projects in this group involve teeth analysis and method development.

The effects of nitrogen dioxide on pulmonary function in patients with asthma and chronic bronchitis are being investigated by studying physiological changes in cardiorespiratory parameters. Similar research is in progress to determine human biochemical and physiological responses to acute photochemical air pollution exposures; the short-term effects of photochemical oxidants on asthmatics, chronic bronchitics, athletes and outdoor workers are being measured.

The childhood health effects of infant exposure to polychlorinated biphenyls (PCBs) are being investigated. The extent to which residues of persistent, fat-soluble PCBs, and chlorinated hydrocarbon pesticides are present in mothers' breast milk is being determined. Cohorts of breast- and formula-fed children are being established for follow-up studies.

The objective of one on-going research project is to develop a simple, rapid, and inexpensive method of determining trace concentrations of toxic energy-related elements in the human body. In another study, more than 1000 teeth from several hundred donors and deceased individuals (including Egyptian mummies) were analyzed for trace and heavy metals; the data are being analyzed statistically for correlations and trends.

5.3.3 Toxicologic Studies

Human toxicologic studies usually involve determining the effects of energy-related pollutants on people under controlled laboratory conditions. Effects on the human pulmonary and nervous systems are currently being investigated.

The effects of various pollutants on human respiratory function are being determined in subjects who are exposed to the pollutants in exposure chambers. After exposure, the subjects are tested for pulmonary function (e.g., spirometry, plethysmographic determination of specific airway conductance, and functional residual capacity), cardiac function, and peripheral circulatory function. The pollutants used in these experiments are sulfuric acid aerosols, respirable sulfates, and low levels of nitrogen dioxide and ozone. In some experiments, factors that might affect toxicity (e.g., temperature, humidity, duration of exposure) are varied for comparison. In other studies, subjects are exposed to trace elements by aerosol inhalation. The pharmacokinetics of pulmonary uptake, deposition, and metabolism of these elements are then studied.

The effects of microwave radiation on neural response and the central nervous system are being studied. Research efforts involve identifying peripheral and central receptor mechanisms that mediate the effects of microwave radiation on brain (e.g., auditory nerve) activity. Electrophysiological and neurochemical methods are being used in this study.

5.3.4 Support/Other

The subcategory of the Human Health Studies discipline that is designated as Support/Other consists of projects that support human health research (i.e., the epidemiological, clinical, and toxicologic studies). Included in this group are projects that entail information gathering, establishment of computerized data bases, development of predictive models, and establishment and maintenance of air-monitoring systems.

The air quality monitoring systems (e.g., CHESS, CHAMP) that were set up under the program are being maintained. These systems support community human health studies by collecting air samples. They are also important in providing the opportunity to evaluate various pollutant monitors and analyzers. In the CLEANS/CLEVER program, stationary and mobile facilities are maintained for the development of a physiological data acquisition system to study the effects of environmental contaminants on human health.

Other support projects involve development of indicators, recommendations, standards, and safety plans. For example, there is research to develop reliable biological indices (e.g., sulfate oxidase enzyme measurement) for use in epidemiological studies. Work is in progress to develop appropriate health-monitoring and testing procedures for personnel in energy-related industries. Other on-going projects should result in recommendations for work practices to protect Alaskan pipeline workers from cold stress, medical and operating safety standards for divers in offshore oil exploration, and occupational exposure to microwave and radio frequency radiation.

Other studies involve establishing computerized data bases, collecting published information (e.g., by literature searches), assessing work practice procedures, and developing programs and models. The Environmental Teratology Information Center (ETIC) maintains a computerized data base that contains more than 14,000 reprints pertinent to the teratogenic potential of environmental agents or contaminants. Work is continuing on the Environmental Mutagen Information Center (EMIC), another computerized data base. EMIC contains more than 22,000 bibliographic entries on the mutagenic effects of energy-related pollutants and 21,000 abstracts that are indexed by agent, organism, and Chemical Abstract Service Registry

(CAS) number. Literature searches are being conducted for various programs in order to: (1) enumerate energy-related occupational health problems; (2) assess energy-related occupational safety and health problems; (3) identify the major health effects, pollutants, and risks from oil shale, tar sands, and geothermal, solar, nuclear, and electric power transmission processes; (4) characterize the industrial hygiene of coal-gasification pilot plants; (5) assess safety in fossil fuel-fired electric power-generating stations (particularly relevant to fire and explosions); and (6) determine the health effects of increased indoor air pollution resulting from energy conservation strategies.

Other support studies involve the development of models. Models now under development include:

- respiratory tract models for determining regional deposition of inhaled particles in smokers, patients with obstructive pulmonary diseases, and various animal species
- physiological kinetic models (compartmental) for carbon monoxide, the lead-calcium system, and the cadmium-zinc system that use nonlinear regression techniques for experiments on uptake and elimination
- stochastic models for external dosage of carbon monoxide and lead and for prediction of body-burden estimates for lead and the alkaline earth metals
- models for assessing the general population health effects that would result from a change in air pollution caused by changing energy requirements so that changes in acute and chronic health conditions can be predicted and correlated with changes in air pollution.

5.4 RISK ASSESSMENT

The scientific discipline of Risk Assessment includes risk assessment research such as identifying problems associated with risk assessment methodologies, performing species-to-species comparisons, and developing low-dose extrapolation techniques.

Research is being conducted to identify the probabilistic and mathematical-statistical problems encountered in the estimation of public health hazards associated with nuclear generator construction, synergistic effects with binary response variables, and competing risks. Studies on species-to-species extrapolation of carcinogenic risk entail quantifying species differences in relation to exposure to particular carcinogenic agents (e.g., dimethylnitrosamine and vinyl chloride). Development of low-dose extrapolation methodology--i.e., estimation of low-dose toxic effects from high-dose experimental data--is based on the Armitage-Doll multistage model for carcinogenesis. This model is being used to analyze dose-response data from experiments in which animals are exposed to various chemical compounds.

The Federal Interagency Energy/Environment R&D Program provided about $750,000 in funds through fiscal year 1978 to the research projects that are included in the scientific discipline of Risk Assessment. This sum constitutes 1.3 percent of the total expenditures during this period for the Health Effects Research Program. Funding for individual research projects in this category ranged from $17,000 to $234,000.

5.5 GENERAL SUPPORT

The General Support category consists of projects that provide support for the research endeavor in the various scientific disciplines. Typical support projects include the collection and preparation of environmental samples for toxicologic testing, the development of an environmental specimen bank, and scientific workshop meetings.

Several projects involve the procurement (e.g., CHAMP air monitoring stations) and preparation of energy-related agents. Other studies are conducted primarily to characterize samples prior to testing (e.g., determination of the nucleation properties of respirable coal dust, development of nuclear magnetic resonance spectroscopic methods for characterizing specific bonding modes of organic and inorganic compounds, and study of photodegradation of absorbed polycyclic arenes).

Projects pertaining to establishment of a National Environmental Specimen Bank include researching analytical methodologies and evaluating methods of sampling, preparing, transporting, and storing biological specimens which might reflect contamination from developing energy technologies. Plans are underway for a chemical repository to store source material from oil shale and coal gasification and liquefaction facilities and particulate effluents from power stations for future chemical analysis. These materials will be available in the future to researchers for use in comparative studies.

Various energy-related workshops have been conducted. Workshop topics include discussion and evaluation of aneuploidy assay systems, screening systems for alternate energy aqueous effluents, and health problems related to recirculation of industrial process exhaust air.

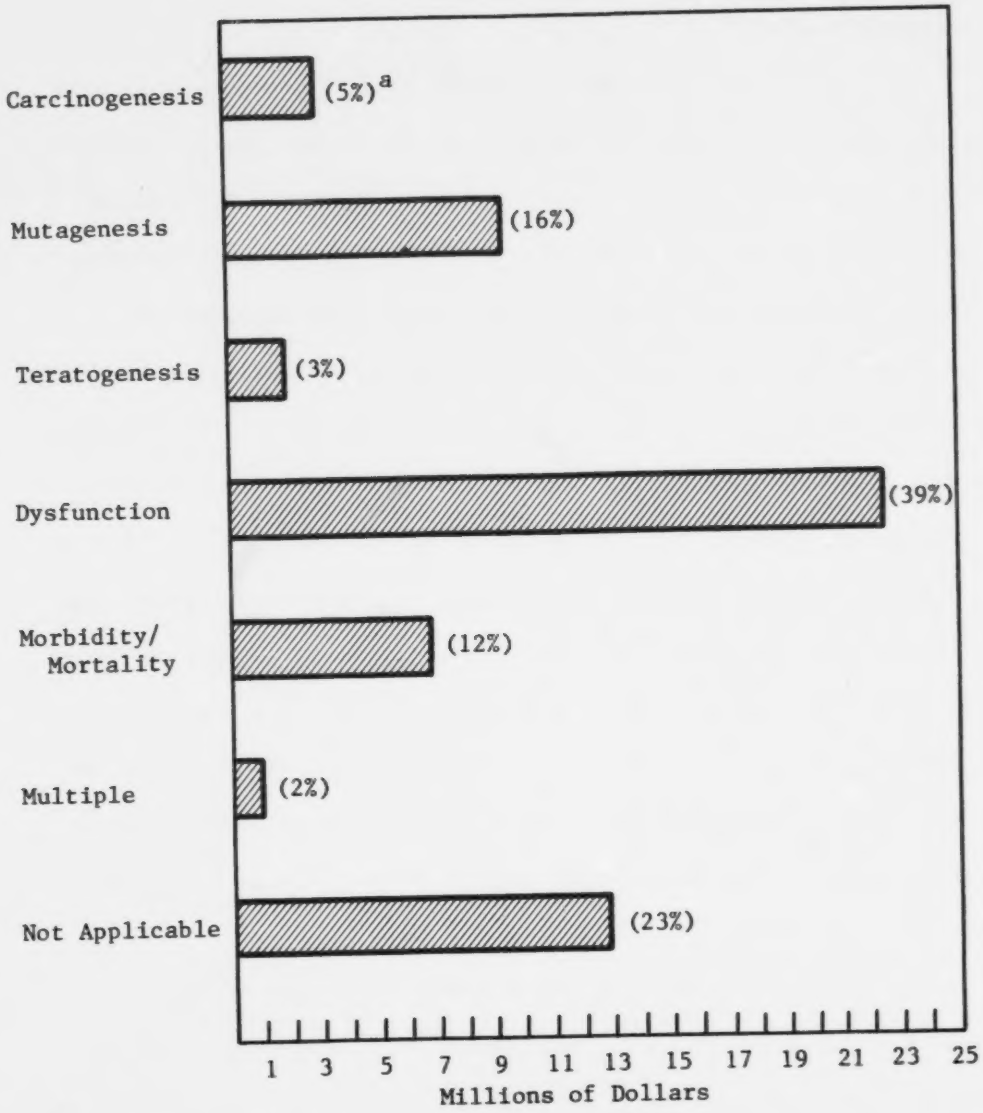
Funding for General Support research projects totaled approximately $3.8 million through fiscal year 1978. This sum constitutes about 7 percent of the total funding for the Health Effects Research Program that was provided during this period by the Federal Interagency Energy/Environment R&D Program. Individual research projects in this category received allocations ranging from $4500 to $627,000.

SECTION 6

PROGRAM REVIEW FROM THE PERSPECTIVE OF BIOLOGICAL ENDPOINTS

Review of the Health Effects Research Program from the perspective of the biological endpoints of the research projects provides a different view of this component of the Federal Interagency Energy/Environment R&D Program. Each research project was assigned to one of the following Biological Endpoint categories: Carcinogenesis, Mutagenesis, Teratogenesis, Dysfunction, Morbidity/ Mortality, Multiple, and Not Applicable. Figure 3 depicts the level of funding and the related level of effort provided each Biological Endpoint category.

Some research projects are designed specifically to examine the types of changes that lead to specific biological endpoints (e.g., carcinogenesis). This is also true of those projects that pertain to biological screening methods, including the development of new screening methods. Other research seeks to correlate disease states and various types of dysfunction with agent exposure so that the factors leading to dysfunction and disease can be determined and preventive measures can be taken to avoid the adverse biological effects of energy-related agents.



[a] Percentages indicate portion of total effort.

FIGURE 3
FUNDING OF PROJECTS BY BIOLOGICAL ENDPOINT CATEGORY

6.1 CARCINOGENESIS

The research projects in the Carcinogenesis category use cells, organs, and whole animals to investigate the morphological, cytological, and biochemical changes that lead to neoplastic transformations. Many of the carcinogenesis screening tests use mutagenesis cellular screening techniques (see Section 6.2 on Mutagenesis).

Much effort is devoted to identifying markers and indicators of preneoplastic transformations. For example, markers of preneoplasia in the respiratory epithelium are being identified, and antigenic responses to squamous carcinomas are being determined.

The mechanisms of tumor production are being investigated, specifically the mechanisms involved in the induction and production of skin tumors by weak and strong carcinogens. The initiation of carcinogenesis by specific energy-related compounds such as benzo(a)-pyrene (BaP) is being investigated. The role of irritant gases in organ susceptibility to tumor production (e.g., in the lung) and in initiation of carcinogenesis is being studied.

The tumorigenic potential of a number of energy-related substances is being determined. New systems are being developed for determining the transforming activity of pollutants. Cloned fish of the species *Poecilia formosa* (Amazon molly) are being developed for use as screening models. Development of rodent cell lines for use in screening to determine the neoplastic potential of energy-related substances is continuing.

The Carcinogenesis biological endpoint category received about $3.1 million in funding through fiscal year 1978, or about 5 percent of the total expenditure for the Health Effects Research Program. Funding for individual research projects in this category ranged from $85,000 to $524,000 during this period.

6.2 MUTAGENESIS

Mutagenesis is the biological endpoint of many of the research projects funded by this Federal Interagency Energy/Environment R&D Program. Energy-related agents are being screened by a variety of test systems (e.g., _Trandescantia_, CHO cells, mouse specific-locus) to detect mutations. In addition, mutagenesis screening techniques are often used to screen substances for potential carcinogenicity because mutagenic alterations in DNA are considered precursors of neoplastic cell transformations.

Mammalian cell mutagenesis assays are used to screen _in situ_ coal gasification effluents and fractionated coal-conversion by-products. The effects of coal and oil shale conversion products on CHO cell cycle kinetics and chromatin structure are being investigated. Research is also being conducted to detect chromosomal aberrations that can be correlated with exposure to photochemical air pollutants and ozone.

Other research projects involve attempts to modify or to develop methodologies for mutagenesis screening and research. Screening methods under development include a polygenic assay for point mutations in mice and methods to detect lethal mutations in mice, to validate short-term mutagenicity tests as predictors of carcinogenic activity, and to modify the host-mediated assay system by using human lymphoid cells.

Mutagenesis studies in the Health Effects Research Program received approximately $9.4 million in funding through fiscal year 1978 from the Federal Interagency Energy/Environment R&D Program. This sum constitutes about 16 percent of the total expenditure for health effects research that was funded by this interagency program. Allocations to individual research projects in this category ranged from $25,000 to $1.5 million.

6.3 TERATOGENESIS

Teratogenesis is the biological endpoint of some of the research projects in the Health Effects Research Program. These projects pertain to the screening of energy-related substances for teratogenic effects.

The distribution of various pollutants in the mother and the fetus and the subsequent effects on mother and fetus are being determined in mice, rats, and hamsters. The factors that affect cross-placental transfer of metallic pollutants and other agents in rats are being determined. The effects of gestational exposure to pollutants on the development of the conceptus are being studied in mice and rabbits by examining structural abnormalities in offspring just before birth.

New screening systems being developed will make it possible to predict the teratogenic potential of various pollutants from alterations in the reproductive process. One of the most sensitive is the mouse oocyte system which is very sensitive to chemical toxicity.

The DNA damage and repair in specific germ cell stages of mammals is being studied. Chemical induction of chromosomal aberrations in mouse germ cells by coal-conversion products is being investigated. Spermatogonia and related cells from the basement membrane of the testes are very sensitive to toxic substances. Changes in the ultrastructure of mouse spermatogonia following pollutant exposure is being correlated with the teratogenic potential of these substances. Abnormalities in sperm shape induced by energy-related hydrocarbons are being studied in laboratory animals as well as man. Defective or abnormal morphology of sperm cells can be linked to specific teratological changes in offspring.

Teratogenesis studies received $2 million through fiscal year 1978 in funding provided by the Federal Interagency Energy/Environment R&D Program. This sum represents about 3 percent of the total funding of the Health Effects Research Program component of the interagency program. Allocations for individual research projects in this category ranged from $25,000 to $340,000 through fiscal year 1978.

6.4 DYSFUNCTION

The Dysfunction category consists of those research projects that pertain to pollutant-caused dysfunction in an organism. The subcategories of Physiological Damage, Metabolic Effects, and Cytotoxic Response reflect the different levels at which dysfunction is manifested.

The sum of $22.6 million was expended through fiscal year 1978 in support of energy-related health effects research projects in the Dysfunction biological endpoint category. This level of funding constitutes 39 percent of the total expenditure for the Health Effects Research Program. Allocations for individual research projects in this category ranged from $20,000 to $921,000 through fiscal year 1978.

6.4.1 Physiological Damage

Damage to an organism that hinders its vital functions or the function of a vital organ is termed physiological damage. The damage that leads to dysfunction is usually related directly to cellular damage in the affected organ. The research projects grouped in this subcategory deal specifically with organ dysfunction and the changes in the vital functions of people and laboratory animals that are caused by exposure to toxic agents.

Most of the research on physiological damage is concerned with developing methods of detecting the types of changes that might be preliminary indicators of chemically induced physiological change/damage. The types of damage indicators being examined include behavioral, structural, biochemical, and immunological.

Many of the research projects in the physiological damage subcategory pertain to the pulmonary system. The effects of air pollutants on lung structure are being determined by scanning electron microscopic (SEM) examination. Pulmonary tissues are also examined by histopathological methods. Regional deposition of inhaled particles in the human lung is being determined, and predictive models that use the patterns of the human tracheobronchial tree are under development. Functional changes in the lung are being correlated with the onset of chronic diseases such as asthma and bronchitis.

Upper respiratory tract clearance mechanisms are being examined in hamster tracheal rings exposed to metallic dusts; from the data, mathematical models to predict lung function changes are being developed. The effects of coal-gasification products, especially particulates, on the defense systems of lungs are being investigated. For example, the ability of the lung clearance mechanisms to remove metal particulates is being related to the lung's susceptibility to bacterial and viral infectious diseases; the objectives are to correlate pneumonia-induced mortality with specific forms of air pollution and diseases in general with environmental conditions. Mathematical models are under development that will predict changes in acute and chronic health conditions on the basis of changes in air pollution using various health and environmental data. Changes in health conditions would be predicted not only for the pulmonary system but also for other vital systems.

The interactions of specific pollutants are being studied to determine additive or synergistic effects. Interactions of vital systems such as the cardiac and pulmonary systems following agent insult at various levels are being analyzed. The effects on the cardiac and pulmonary systems, with special emphasis on the peripheral circulatory function in adults, are being determined for exposures to nitrogen dioxide and ozone at low concentrations. The acute and chronic effects of the inhalation of fly ash and mixtures of carbon monoxide and sulfur and nitrogen dioxides are being determined.

The effects on mammalian brain development of generations of exposure to low-level radiation are being ascertained. Postnatal development and function of the central nervous system in monkeys after their exposure to tritiated water during the period from conception to birth and weaning are being assessed.

Neurotoxicology is a rapidly developing field that needs new testing and screening methods. One new method uses "seeing computers"--i.e., computer-based on-line closed circuit television monitors that feed behavioral response patterns in experimental animals into a computer for analysis and comparison with baseline response data from control animals. Studies are being made of behavioral changes that result from exposure to metal dusts, coal conversion products, hydrocarbons and other pollutants. With such automated systems, behavioral testing is less time-consuming and more reliable. Behavioral testing and other neurotoxicologic studies of the effects of exposure to chemical agents, electrical fields, and microwave radiation are being conducted. For example, the behavioral effects of prenatal exposure to microwaves and the effects of microwave radiation on brain activity involving the peripheral and central receptor mechanisms are being investigated.

6.4.2 Metabolic Effects

All the research projects that involve metabolism studies are grouped into the metabolic effects subcategory. The functions of cells, organs, and living organisms all depend on chemical reactions, i.e., metabolism. These chemical reactions allow cells to perform life-sustaining functions such as reproducing, obtaining nourishment, growing, expressing genetic characteristics, and providing defense. This is true for all living things including man; the only difference is that usually the more complex the organism, the more complex the chemical reactions involved. Many substances occur naturally in living organisms and are necessary for the organism to remain viable. However, energy-related technology introduces substances into the environment that affect the chemical reactions necessary for life. Changes in metabolic reactions caused by environmental agents are receiving considerable attention.

The biochemical effects on the macromolecular metabolism of the lung of trace metals such as cadmium, nickel, lead, and arsenic are being investigated. The effects of metals on membrane constituents of the lung and other organs are of special interest. Also being studied are the effects of hydrocarbons, sulfur dioxide, and related fossil fuel pollutants on lung membranes, particularly during development from birth to adulthood. The metabolism and accumulation of hazardous agents in lung tissues explains the level of damage seen in lungs following exposure and often also the degree of toxicity of the agent. The molecular mechanisms involved in the initiation of cancer and other diseases by specific energy-related pollutants are being investigated. Repair and recovery mechanisms are also being studied; if these mechanisms remain active and viable after chemical insult, the organ may recover and may construct defense mechanisms against future pollutant insult.

Methods are being developed to quantify the levels of various pollutants in tissues, fluids, fat, and other biological samples. These data provide information that is necessary for determining metabolic pathways. Factors such as diet that affect metabolic pathways in various organs are being assessed; diet might affect the gastrointestinal absorption of cadmium, for example. Sites that store chemical agents are being analyzed so that storage information can be used in determining exposure histories. In one study, teeth are being analyzed for lead to determine the history of lead exposure levels in the community. Radioactively labeled compounds are being synthesized for use in animal metabolism studies so that concentrations of these compounds in body tissues and fluids can be determined accurately and body clearance rates can be estimated.

Metabolic activation of specific classes of substances is being studied because many agents require metabolic activation before they can exhibit toxicity. The enzymatic characteristics of the process of metabolic activation of carcinogens and subsequent DNA binding are being investigated. The relationship between the metabolism of carcinogens in alveolar macrophages and the induction of lung cancer is being determined. The potential synergism of two pollutants such as nitrogen dioxide and ozone are being investigated so that the mode of toxic action of nitrogen dioxide can better be understood.

Receiving special consideration are the metabolic pathways of metals, their sites of localization, and transfer mechanisms. For example, the biochemistry of methyl mercury and its ability to bind to DNA are being investigated. The neurotoxicity of metals is being studied from the aspect of their metabolism and their effects on brain biochemistry. The metabolism of metals and other pollutants in various cell lines is being investigated. New epithelial cell lines are being developed; these cell lines have special characteristics and can activate specific classes of energy-related agents and thus should prove useful in future screening programs.

6.4.3 Cytotoxic Response

The research projects that are grouped in the cytotoxic response subcategory deal with cellular toxicity (cytotoxicity). Cells reproduce, grow, and die, and during their lifespan they may undergo genetic alterations that affect the function of the metabolic, damage, and repair mechanisms. These mechanisms and other cellular reactions can be monitored for evidence of cytotoxic response to exposure to toxic substances.

Cellular systems provide an important screening tool for determining the relative toxicities of pollutants because they are less complex than whole animal models. Many studies are directed toward developing new cell lines and cellular systems for screening. Others are improving present screening procedures and developing new methodologies that will improve their efficiency and reliability. Automated flow systems are being developed to perform chromosomal analysis, to check for karyotype stability in cell lines, to profile cytochemical markers, and to detect other early cell changes. These new techniques will shorten analysis time in screening procedures. Scanning electron microscopic (SEM) procedures are being developed to examine alveolar macrophage cultures for cytological changes that constitute the effects of air pollutants on the pulmonary system. Hyperplastic, metaplastic, and neoplastic changes in epithelial cell lines caused by toxic chemicals can be detected by microscopic examination. These cytotoxic responses are important for determining the hazards of specific environmental agents.

The effect of toxic agents on the regulatory macromolecules of mammalian cells is of special interest. Molecular damage to DNA, auto-oxidation of lipids in biomembranes, the effects of enzyme alterations and inhibitions on the synthesis of protein, phagocytic activity, and collagen synthesis are all being studied. Efforts are being made to determine the ability of cells to metabolize foreign agents such as metals and to estimate the agents' rates of binding to various cell components. Specifically, the cofactors involved in the conjugation of carcinogens with DNA and other regulatory macromolecules are being determined. The effects on the cell of combinations of agents such as ultraviolet light and polycyclic aromatic hydrocarbons are being studied. The effects of toxic agents on neuronal communication in the central nervous system are being investigated by studying neurons in tissue culture. The promoting role of estrogens in the hormonal regulation of chemical carcinogenesis is being investigated so that the induction of endometrial adenocarinoma by estrogens can be better understood.

6.5 MORBIDITY/MORTALITY

The Morbidity/Mortality biological endpoint category contains research projects that are concerned with human morbidity and mortality related to the energy industries. Many of these studies pertain to occupational safety and health.

The subjects of occupational health studies include oil shale workers; deep-sea divers; Alaskan pipeline workers; petroleum production workers; miners; coal-cleaning workers; solar energy workers; Tennessee Valley Authority employees; and workers in the sulfuric acid, sulfate, nitrate, clay fibers, fibrous glass, mineral wool, and coal liquefaction and gasification industries.

In these studies of workers in energy-related fields, the workers' occupational histories are recorded, physical examinations are conducted on a routine basis, and death certificates are examined. More specifically, petroleum production workers, miners, and coal-cleaning workers are being examined for evidence of physical and chemical skin irritation. Workers exposed to insulation materials (e.g., clay, glass, and mineral wool fibers) are being studied for lung dysfunction and disease. Alaskan pipeline workers are being examined to determine the health effects of cold stress.

In addition, acute and chronic toxicities to humans and the safe exposure levels of several energy-related hazardous materials are being estimated.

Epidemiological studies include studies of the health effects resulting from the deterioration in air quality that is attributable to fossil fuel power generation, the health effects of increased indoor air pollution, and the childhood health effects of infant exposure to PCBs in mothers' milk. A survey of people using water supplies that originate in areas used for coal extraction is in progress.

Morbidity/Mortality studies received approximately $6.8 million in funding through fiscal year 1978, or about 12 percent of the funding for the energy-related health effects research that was provided by the Federal Interagency Energy/Environment R&D Program. Allocations through fiscal year 1978 for individual research projects in this category ranged from $8000 to nearly $1 million.

6.6 MULTIPLE

A few research projects have been grouped in the Multiple biological endpoint category. Each of these projects examines various effects of given energy-related pollutants and, therefore, deals with more than one biological endpoint.

These projects include studies of the hematologic and mutagenic effects of arsine, the teratogenic and mutagenic effects of trace metals, and the mutagenic and carcinogenic effects of hydrocarbons on cultured mammalian cells. In other studies, the chemistry, cytotoxicity, mutagenicity, and pulmonary effects of stack emission condensate samples are being determined.

Funding for the Multiple biological endpoint category amounted to about $1 million through fiscal year 1978. This level of funding constitutes about 2 percent of the total expenditure for the Health Effects Research Program. Individual research projects in this category received allocations that ranged from $36,000 to $475,000.

6.7 NOT APPLICABLE

Those health effects research projects that do not involve specific biological endpoints are grouped in the Not Applicable category. These projects are usually supportive in nature. Some entail information gathering, establishing computerized data bases, or developing predictive models.

The objectives of other projects in this category are to establish a national environmental specimen bank, organize workshops, develop risk assessment methodologies and safety recommendations, and prepare environmental samples for testing. Some projects involve maintaining air quality monitoring stations (e.g., CHESS and CHAMP) in support of human health studies and maintaining stationary and mobile facilities (e.g., CLEANS/CLEVER) for developing a physiological data acquisition system.

The Not Applicable category of research projects received approximately $13.1 million through fiscal year 1978, a level of funding that represents about 23 percent of the total support for the Health Effects Research Program. Expenditures for individual research projects in this category ranged from $4500 to about $1.6 million.

SECTION 7

PROGRAM REVIEW FROM THE PERSPECTIVE OF AGENTS/POLLUTANTS

In this section, the Health Effects Research Program component of the Federal Interagency Energy/Environment R&D Program is reviewed in terms of the agents and pollutants that derive from the various energy technology processes. For the purposes of this review, seven agent/pollutant categories were selected:

- Organic--includes substances such as hydrocarbons, sodium acetate, and methyl mercury
- Inorganic--includes inorganic compounds and substances such as fly ash, particulates, fibers, and asbestos
- Elemental--includes elements such as metals (e.g., iron, lead, and molybdenum) and oxygen (i.e., ozone)
- Physical--includes physical agents such as radiation (e.g., ultraviolet, microwave, and radio frequency) and temperature
- Energy-related--includes nonspecified substances derived from energy technologies
- Multiple--includes substances such as mixed carcinogens and photochemical air pollutants
- Not Applicable--for those research projects that are not concerned with any specific agent or pollutant as a test substance (e.g., occupational safety studies, workshops, data bases, and specimen banks).

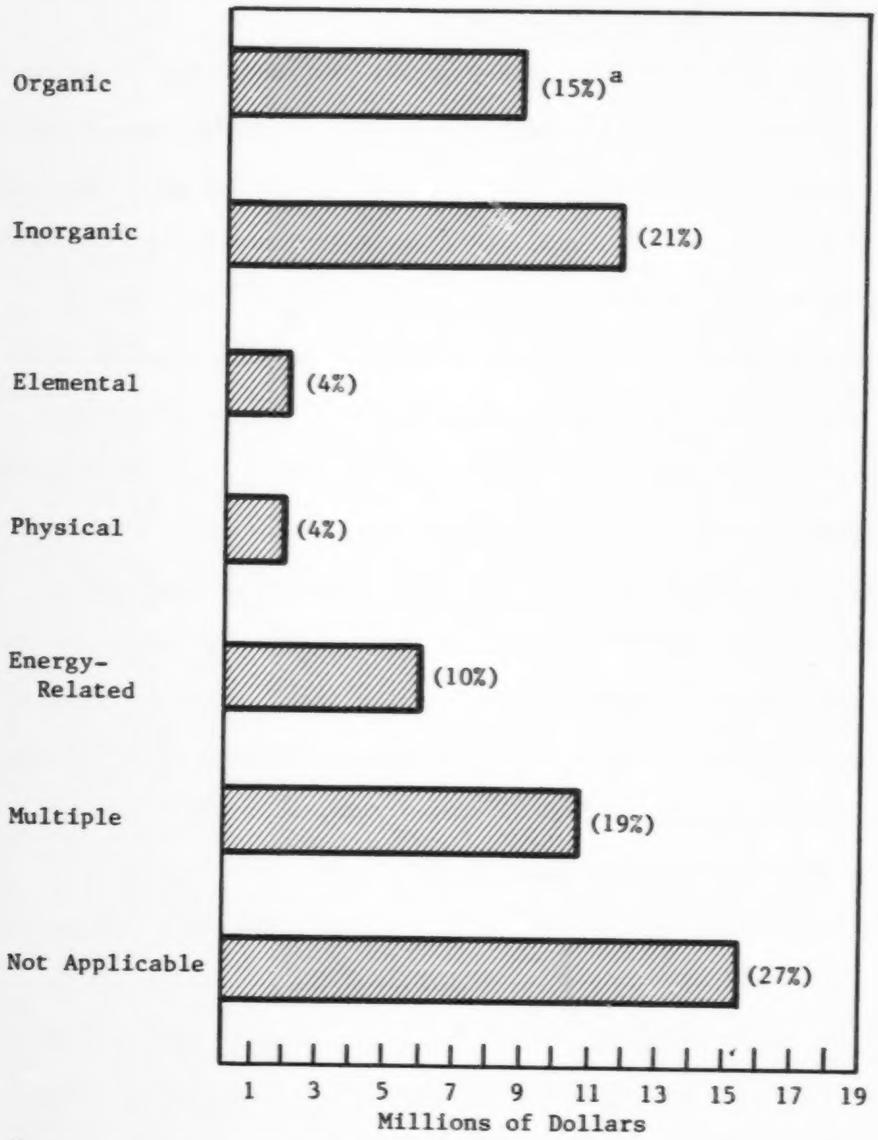
Each research project was assigned to the appropriate agent/pollutant category.

The funding provided each agent/pollutant category through fiscal year 1978 and the relative levels of effort are indicated in Figure 4.

7.1 ORGANIC POLLUTANTS

Organic substances are classically defined as those that contain carbon. For the purposes of this discussion, all carbon-containing substances including organometallic compounds are classified as organic pollutants. Many of the products and by-products of energy-related technology processes are organic in nature, and they are used/tested in many of the health effects research projects. These studies involve developing testing methods, screening suspected toxic substances, determining relationships between agents, and determining the mode of toxication.

Polycyclic aromatic hydrocarbons (PAH) are derived from several energy technologies, and many are carcinogenic. These compounds are being subjected to a variety of tests. Research is in progress to develop screening systems suitable for PAH. These include a tracheal graft model system and a bacteriophage system for evaluating the toxicity and carcinogenicity of PAH. In other PAH research projects, the investigators are trying to identify the susceptible positions on PAH substrates that react with nucleic acids, to determine the damage and repair mechanisms for DNA in specific germ cell stages of mammals following *in vivo* exposure to PAH, and to determine other biological damage mechanisms of PAH. The carcinogenicity of PAH and the



[a]Percentages indicate portion of total effort.

FIGURE 4
FUNDING OF PROJECTS BY AGENT/POLLUTANT CATEGORY

regulatory role of estrogens and other hormones in the induction of carcinogenesis are being studied.

Several studies pertain to halogenated hydrocarbons. Research on PCBs involves examination of mother's milk for PCBs, determination of the childhood health effects of PCB exposure in infancy, and study of the pharmacodynamics of PCBs. Studies of hexabrominated biphenyls involve determination of their neurotoxicity to mice and rats.

Benzo(a)pyrene (BaP) is being studied in several research projects. One involves research on carcinogenesis initiation and its analogy to other biological responses such as mutations. A pulmonary carcinogenicity testing system is being used to ascertain whether there is a correlation between cell proliferation and lung tumor susceptibility and whether susceptibility to BaP is age dependent in mice. The metabolic capability of _in vitro_ test systems to produce the same metabolically active carcinogenic metabolites of BaP as are formed _in vivo_ is being examined. The structure of BaP metabolites bound to DNA of _Salmonella_ is being determined.

Polycyclic arenes are under study, specifically their photodegradation. The effects of carbon monoxide on neurons in tissue culture are being studied. Research projects dealing with organometallic compounds include studies of the effects of cadmium acetate on the ultrastructure of type A spermatogonia and the binding of methyl mercury with DNA.

A number of organic substances and mixtures are being subjected to toxicologic screening. For example, potential air pollutants are being screened for carcinogenicity with the BALB/C3T3 and C3H/10T 1/2 bioassay systems, for gene mutations in mouse germ cells (*in vitro*), and for carcinogenesis and virus activation (*in vitro*). Organic products and by-products of coal and oil utilization are being studied to determine the functional and quantitative changes that they induce in immunocompetent cells. Environmental chemicals are being tested to detect their genotoxic effects on cultured liver cells.

Other research projects on nonspecified organic substances involve the development of testing methodologies and the determination of response relationships. These studies include development of a modified host-mediated assay using human lymphoid cells, development of a DNA repair system for monitoring human health effects, and determination of the relationship between carcinogen metabolism in the alveolar macrophage and the induction of lung cancer. Coal conversion and utilization products are being tested in monkeys; an automated behavioral testing system is being developed for evaluation of the toxicity of these products on the central nervous system. Environmental mutagenic agents are being screened by both *in vitro* and *in vivo* testing methods. The study of environmental carcinogens will be aided by the development of permanent epithelial cell lines for use in determining toxic/carcinogenic effects.

Some research projects are concerned with the combined effects of both organic and nonorganic substances. Those that combine organic and inorganic substances include the following studies: determination of the effects of whole animal exposure to acid mists on pulmonary metabolism of BaP in isolated perfused rabbit lung; development of faster, more efficient, and less costly methods of determining teratogenic changes that result from exposure to dipterex and asbestos; determination of the role of irritant gases on the susceptibility of respiratory tract epithelium to tumor induction; and assessment of the effects of mixed pollutants (e.g., sulfur and nitrogen dioxides and formaldehyde) on alveolar macrophages by biophysical and biochemical techniques. The chemical toxicity of PAH, chloroform, sodium sulfite, lead and platinum is being monitored by the mouse oocyte system. One research project is screening organic substances and physical agents by teratology test systems. A study of metal-binding components of emissions from mobile and stationary energy sources is characterizing them chemically and determining their toxicity.

The Organic pollutants category received approximately $8.7 million through fiscal year 1978, or 15 percent of the funding for the Health Effects Research Program. Expenditures for individual research projects in this category ranged from $25,000 to $719,000.

7.2 INORGANIC POLLUTANTS AND AGENTS

For the purposes of this review, the Inorganic pollutants and agents category includes agents such as fly ash, particulates, and fibers in addition to inorganic compounds.

Various inorganic sulfur compounds are being studied. One research project is a study of the effects of respirable sulfates and sulfuric acid mists on the respiratory function of normal human subjects. Occupational exposures to sulfuric acid and sulfur dioxide are being examined in epidemiological studies. The effects of hydrogen sulfide on neurons in tissue culture are being examined in another study.

Nitrogen compounds--nitrogen dioxide in particular--are being examined in various research projects. Epidemiological studies are in progress of persons who are/were occupationally exposed to nitric acid and to nitrogen dioxide from fossil fuel sources. The effects of nitrogen dioxide on the lung are being examined in several research projects; these include studies of the auto-oxidation of lung biomembrane lipids and surfactants that is initiated by nitrogen dioxide and its inhibition by antioxidants, the effects of vitamin A on lung cell kinetics, and the alteration of nitrogen dioxide toxicity by vitamin E and lipids. The effects of nitrogen oxides on membranes (e.g., liposomes, lecithin multilayers, and biomembranes) are being determined by electron spin resource spectrometry.

A few of the health effects research projects pertain to inorganic metal compounds. The cytotoxicity of selected metallic sulfates is being assessed. Metal oxides are present in emissions from fossil fuel combustion, and the role of alveolar macrophages in the distribution of inhaled metal oxides is being studied. The hematologic and mutagenic effects of arsine are being determined.

Several research projects pertain to airborne particulate matter. Particulate samples are being procured, prepared, and characterized for toxicologic testing. Particulate material is screened for potential hazard by an alveolar macrophage test system. Models are being developed to predict the deposition of inhaled particles in regions of the human lung. The effects of prolonged inhalation of nickle-enriched fly ash are being investigated in Syrian golden hamsters.

Mineral wool fibers, small fibrous glass fibers, and clay fibers in insulating materials are the agents under study in several projects. Occupational exposure, mortality, and industrial hygiene studies are being conducted of workers in these industries.

Some of the research projects are examining the effects of simultaneous exposure to pollutants/agents from more than one category. Those that involve inorganic and organic pollutants were discussed under Organic pollutants (Section 7.1). Two other projects involve one other category in addition to Inorganic pollutants. In one of these, the effects of nitrogen dioxide and environmental trace metals (i.e., elemental pollutants) on lung metabolism are being investigated. In the other, the effects of nitrogen dioxide during heat stress (a Physical agent) are being assessed by monitoring the cardiac, pulmonary, and peripheral circulatory functions in adult male volunteers.

Funding for research projects in the Inorganic pollutants and agents category was approximately $12.2 million through fiscal year

1978. This sum constitutes 21 percent of the total funding for the Health Effects Research Program that was provided by the Federal Interagency Energy/Environment R&D Program. The level of funding for individual research projects in this category ranged from $35,000 to $692,000.

7.3 ELEMENTAL POLLUTANTS

For the purpose of this review, unconjugated metals and elemental compounds such as ozone are grouped in the Elemental pollutants category.

Several research projects pertain to lead. Among these are studies of the concentration of lead in the teeth of children and the interaction of lead with body tissues and fluids. Lead is usually included when a group of metals is under study (see below). The combined toxic effect of lead and platinum with several compounds is being studied (see discussion under Organic pollutants, Section 7.1).

Cadmium is the object of study in several research projects. These include determination of the effects of cadmium on karyotype stability in CHO cells and on growth and metabolism of CHO cells exposed to low levels of cadmium. The interactions of cadmium with pulmonary alveolar macrophages are being studied.

Some projects involve screening or testing various metals. For example, methods are being developed for the use of teeth as indicators of the tissue dose of various metals. Cadmium, mercury, nickel, arsenic, lead, and platinum are being studied to determine their biochemical effects on pulmonary macromolecular metabolism.

Ozone is the subject of several health effects studies. One, a study of occupational exposure of welder trainees to ozone, entails examination of peripheral blood lymphocytes for chromosomal aberrations. In a study of ozone toxicity to lung lipids, the effects of vitamin E on this toxicity are being examined. The combined effect of ozone and trace metals on lung metabolism is the subject of another study. One research project pertains to the effects on adult males of exposure to ozone during heat stress, as monitored by changes in their cardiac, pulmonary, and peripheral circulatory functions.

Funding for the research projects that are grouped in the Elemental pollutants category amounted to approximately $2.3 million through fiscal year 1978. This sum constitutes 4 percent of the total funding for the Health Effects Research Program. Expenditures for individual research projects in this category ranged from $35,000 to $921,000.

7.4 PHYSICAL AGENTS

The Physical agents that are being studied in the Health Effects Research Program are radiation and temperature. Several types of radiation--microwave, electrical field, radio frequency, light, and radioisotope--are being studied. Temperature studies include the effects of both cold and heat stress.

Several research projects pertain to microwave radiation and its effect on the central nervous system. Investigators are examining the effect of microwave radiation on neural response; its effects on the behavior and reproduction of monkeys, rats, and other animals; and the peripheral and central receptor mechanisms that mediate the effects of microwave radiation on brain activity. A criteria document for occupational exposure to microwave and radio-frequency radiation was developed; it presents recommendations on the control of hazards associated with these exposures.

Research on the effects of electrical field radiation includes behavioral testing, neurotoxicologic studies, and monitoring of reproductive and biochemical effects. In addition, the genetic effects of electrical field radiation are being studied by assessing the frequency of chromosomal aberrations in offspring of exposed *Drosophila*.

Research on light involves both visible and ultraviolet light. The role of visible and ultraviolet light in synergism with PAH is under study. In particular, the mechanisms of skin tumor initiation are being investigated.

Radioisotope studies use tritiated water to expose monkeys to radiation during the period from conception to birth and weaning. Postnatal development and function of the central nervous system are monitored in the offspring.

The effects of temperature extremes are being studied in two research projects. One, involving cold stress, is an industrial hygiene study that was designed to determine the work practices needed to protect Alaskan pipeline workers. The other is a study of heat stress; specifically, the effects on adult males of exposure to nitrogen dioxide, ozone, and ambient air during heat stress. The cardiac, pulmonary, and peripheral circulatory functions of the subjects are being monitored.

Expenditures for the research projects that involve Physical agents amounted to $2.1 million through fiscal year 1978. This sum represents about 4 percent of the total funding for the Health Effects Research Program. The level of funding for individual research projects in this category ranged from $9000 to $891,000.

7.5 ENERGY-RELATED POLLUTANTS

The general, undefined pollutants that are derived from energy-related sources are included in this category. Although a few are nonspecific, some are defined as the by-products present in the emissions and effluents from alternate energy technology processes.

Crude material from nonspecified alternate energy sources will be screened for potential carcinogenesis using bacterial mutagenesis testing methods that are now under development. The effects of coal and oil shale conversion products on cell cycle kinetics and chromatin structure are being determined. Several research projects involve testing effluents and emissions from alternate energy technology processes. For example, studies are being conducted with products released from coal conversion (e.g., gasification and liquefaction) processes in order to determine mammalian cell mutagenesis, evaluate dose-response relationships for immune system enzyme levels, determine molecular damage to DNA and proteins, assay the mutagenicity of fractionated coal conversion products, and develop a nonmammalian (fish) model for quantitative evaluation of carcinogenicity.

Cocarcinogenic agents produced during coal and oil shale processing and from low-Btu gasifiers are being screened by *in vitro* methods. The effects of chemical toxicants associated with the production and consumption of fuel on the physiology and pathophysiology of phagocytic cells are being determined. Undefined pollutants from various energy technology processes are being subjected to quantitative mutagenesis testing in mammalian cellular systems. The interactions of various undefined pollutants and their relationship to the causation of pulmonary disease are being investigated.

Several projects involve energy-related air pollutants. The effects of exposure to photochemical air pollutants are being studied by examining the resultant chromosomal aberrations in peripheral lymphocytes of man. *In vitro* screening of selected air pollutants for potential carcinogenicity uses microbial systems. Individual pollutant particles in lung tissue are being analyzed by multimode scanning electron microscopy. Emissions from power plants that burn eastern and western coals are being characterized, evaluated toxicologically, and compared.

Projects in the category of Energy-Related pollutants received approximately $6.1 million in funds through fiscal year 1978. This sum constitutes about 10 percent of the total funding provided for the Health Effects Research Program. The level of funding for individual research projects in this category ranged from $30,000 to $530,000.

7.6 MULTIPLE POLLUTANTS

The Multiple pollutants category consists of nonspecific pollutants (e.g., environmental mutagens) and mixtures of pollutants (e.g., air pollutants).

The effects of environmental mutagens on the genotypes of higher animals are being monitored. The tumor response evoked by exposure to mixed carcinogens is being studied to determine the synergistic action of these substances. DNA is being exposed to chemical carcinogens and radiation for study of synergistic effects and the DNA repair mechanisms.

Pollutants present in drinking water are being studied. Areas where drinking water supplies are contaminated with energy production by-products are being identified, an epidemiological study of the people using these water supplies is in progress, and morbidity/mortality information and water quality data are being correlated to identify any adverse health effects that are attributable to the energy-related pollutants.

Various research projects pertain to air pollutants. The pulmonary effects of exposure to toxic gases and particulates are being investigated through studies of the biochemical mechanisms of pulmonary injury and the biology and pathobiology of pulmonary epithelial cells. The effects of acute exposure to petrochemical air pollutants on biochemical and physiological responses in man are being determined by investigating the interaction of atmospheric contaminants with respiratory system components and receptors at both the biochemical and functional levels. Changes in air pollution that will result from changing energy requirements are being determined, and models are being developed for use in predicting the health effects that such changes in air pollution will produce in the general population. The effects of increased indoor air pollution on human health are being studied; these changes in air pollution levels are attributable to energy conservation measures. The effects of ambient air (compared with exposures to nitrogen dioxide and ozone) during heat stress are being studied in adult volunteers.

Approximately $10.9 million was funded to research projects in the Multiple pollutants category through fiscal year 1978. This level of funding constitutes about 19 percent of the total funding for the Health Effects Research Program. Expenditures for individual research projects in this category ranged from $8000 to $1.5 million.

7.7 NOT APPLICABLE

The Not Applicable category consists of those health effects research projects in which no specific agent or pollutant is being tested or studied. Many of these projects involve information-gathering tasks that include the establishment of computerized data bases, establishment and maintenance of air quality monitoring stations, and maintenance of data acquisition systems.

Other projects provide different types of support for the Health Effects Research Program. Some of these involve the continued development of risk assessment methodologies and mathematical models. Other projects entail the development and/or improvement of laboratory techniques for use in research; among these techniques are identification of markers for preneoplasia in respiratory epithelium, detection of point mutations in somatic cells, scoring of chemical transformation in C3H/10T 1/2 cells, and detection of early changes in lung cell cytology by flow-systems analysis.

Funding for research projects in the Not Applicable category amounted to approximately $15.6 million through fiscal year 1978, which is 27 percent of the total funding for the Health Effects Research Program. The level of funding for individual research projects in this category ranged from $4500 to $2.6 million.

APPENDIX

LIST OF PROJECTS IN THE HEALTH EFFECTS RESEARCH PROGRAM

KING-MUIR CATEGORY #1

PROJECT	PRINCIPAL INVESTIGATOR	AFFILIATION
Chemical Characterization and Toxicity of Metal-Binding Components of Emissions from Mobile and Stationary Energy Sources	Finelli	University of Cincinnati
Comparative Toxicological Evaluation of Emissions from Power Plants Using Eastern vs. Western Coals	Finelli	University of Cincinnati
Determination of the Influence of Materials Concerned with the Extraction of Ores	Palekar	Northrop Services
Identify Hazardous Agents Associated with Nonnuclear Energy Technologies Using New and Available Biological Screening and Test Systems	Palekar/Carter	Northrop Services/Oak Ridge
Cellular Toxicity of Selected Metallic Sulfates: Studies on the Rabbit Alveolar Macrophages *In Vitro*	Campbell	Northrop Services
Implementation of Screening Tests for Potentially Hazardous Airborne Particulate Materials Using Alveolar Macrophage Test System	Garrett	Northrop Services
Calibrate Cyclone Used to Obtain Large Quantities of Size-Segregated Particulate	[a]—	Southern Research Institute
Field Testing--Application of Improved Combustion Technology to Power Generation Combustion Systems	Menny	Exxon R & E
Comparison of Pulmonary Carcinogenicity of Known Carcinogens with and without Added H_2SO_4 Mists, Airborne Respirable Particles and Gases	Laskin/Sellakumar	New York University
Development of Methods for Determination of Carcinogenesis by Bacterial Mutagenesis Employing Crude Material from Alternate Energy Sources	Commoner	Washington University
Studies to Improve the Reliability and Sensitivity of Bacterial Mutagenesis as a Screen for Environmental Carcinogens	Commoner	Washington University
Development of Automated Behavioral Testing Methodologies for Study of Effects of Coal Conversion and Utilization Products	Buck	Iowa State University

KING-MUIR CATEGORY #1 (Continued)

PROJECT	PRINCIPAL INVESTIGATOR	AFFILIATION
Procurement and Characterization of Refined Particles:		
Preparation and Characterization of Fine Particulate Environmental Contaminants for Biological Experimentation	Knudson/Harwood	IIT Research Institute
Chemical Characterization and Specimen Preparation of Fibrous Amphibole and Refined Particles	Walia/Yamante	IIT Research Institute
Collection and Characterization of Naturally Occurring Airborne Particulates	–	National Bureau of Standards
In Vitro Screening of Selected Air Pollutants for Potential Carcinogenicity Using Microbial Systems	Little/Pellasari	Research Triangle Institute
Detection of Genotoxic Effects of Environmental Chemicals in Cultured Liver Cells	Williams	American Health Foundation
The Need for Combined *In Vitro* and *In Vivo* Systems in Mutagenicity Screening: An Analysis of 47[illegible] Presumable Carcinogens	Legator	University of Texas
Environmental Mutagenic Studies Utilizing a *Drosophila* Test System	Baum	Brookhaven National Laboratories
In Vivo Methods for Assessing Neurotoxicity	Borchein	University of Cincinnati
Determine the Relative Cellular Toxicity of Selected Compounds Including Metallic Chlorides, Sulfates, Sulfides, Organic and Other Pure Chemicals and Crude Samples Obtained from Stationary Sources and Ambient Air	–	Northrop Services
Quantitative Mutagenesis Testing in Mammalian Cellular Systems	Hatch/Carver	Lawrence Livermore Laboratory
Mammalian Cell Mutagenesis Assay for *In Situ* Coal Gasification Effluents	Hatch/Carver	Lawrence Livermore Laboratory
Sperm Shape Abnormalities Induced by Energy-Related Hydrocarbons and Industrial Chemicals	Wyrobek	Lawrence Livermore Laboratory
A Bacteriophage System for Screening of Carcinogenic Polycyclic Aromatic Hydrocarbons	Weiss	Franklin McLean Memorial Research Institute
Effects of Energy-Related Pollutants on Carcinogenesis or Assessment of Carcinogenic Risk from Energy-Related Environmental Pollutants--Rodent Model	Fry	Argonne National Laboratory
Development of *In Vitro* Screening Assay for Cocarcinogenic Agents Produced during Coal and Oil Shale Processing	Byfield	UCLA Laboratory of Nuclear Medicine and Radiation Biology
Detection of Early Changes in Lung Cell Cytology by Flow-Systems Analysis Techniques	Steinkamp	Los Alamos Scientific Laboratory
Analysis of Effects of Energy-Related Toxic Agents on Karyotype Stability in Mammalian Cells	Deaven	Los Alamos Scientific Laboratory

KING-MUIR CATEGORY #1 (Concluded)

PROJECT	PRINCIPAL INVESTIGATOR	AFFILIATION
In Vitro Assay for Carcinogens and Virus Activation	Tennant	Oak Ridge National Laboratory
Mutagenicity Assay of Fractionated Coal-Conversion Products	Epler	Oak Ridge National Laboratory
In Vivo Screening for Gene Mutations in Mouse Germ Cells and Somatic Cells	Russell	Oak Ridge National Laboratory
In Vitro Chemical Cocarcinogenesis of Hormones and Polycyclic Aromatic Hydrocarbons	Gerschenson	UCLA Laboratory of Nuclear Medicine and Radiation Biology
Chemical Induction of Chromosomal Aberrations in Mouse Germ Cells by Coal Conversion Products	Generoso	Oak Ridge National Laboratory
Biological Screening Study of Low BTU Industrial Gasifiers	-	Department of Energy
Biological Screening Study of H-Coal Liquefaction Operations	-	Department of Energy

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KING-MUIR CATEGORY #2

PROJECT	PRINCIPAL INVESTIGATOR	AFFILIATION
The Effects of Cadmium on the Ultrastructure of Type A Spermatogonia	Jordan	Grambling College
Biological Effects of Catalytic Emission Components and Effects of Energy Consumption Related Trace Metals on Pulmonary Macromolecular Metabolism	Bhatnager	University of California (S.F.), School of Dentistry
Development of Cellular Model System to Determine Cytotoxicity from Alternate Energy Sources	Bowers	Rockefeller University
Development of Bioindicators of SO_2 and NO_2 Exposure	Bollinger/Geller	Southwest Foundation for Research and Education
Development of Physiological and/or Biochemical Indicators for Use in Epidemiologic Studies	Rajagopalan	Duke University
Enzymatic Characterization of Metabolic Activation and DNA Binding of Presumptive Carcinogens in Short-Term Assay Systems for Environmental Carcinogens	Weinstein	Columbia University
Application of Automated Behavioral Testing System to Monkeys Exposed to Coal Conversion Pollutants	Lloyd	Iowa State University
Workshop on "Screening Systems for Alternate Energy Effluents"	Aldridge	Kappa System, Inc.
Development of Test Systems to Assess Potential Toxicity and Neoplastic Transformation--Improved Scoring of Chemical Transformation of C3H/10T½ Cells	Heidelberger	University of Southern California
Development of Methods for Determination of Potential Carcinogenicity in Neoplastic Transformation System Employing Crude Material from Alternate Energy Sources	Schrechtman	Microbiological Associates
Electroencephalographic and Behavioral Studies of Rats During Long-Term Continuous Exposure to SO_2 and Particulate Matter	Cooper	University of Cincinnati
Chromosomal Aberrations in Peripheral Lymphocytes of Man as a Function of Exposure to Photochemical Air Pollutants	-	University of Utah
Chromosomal Abnormalities Among Welder Trainees	Bloom	Columbia University
To Evaluate Existing and Improved Methods for Sampling, Transport, Storage, and Analysis of Biological Specimens Which Might Serve as Indicators of Contamination by Effluents from Energy Technologies	-	National Bureau of Standards
Development of Cytochemical Markers for Cell Transformation and Carcinogenesis	Mayall	Lawrence Livermore Laboratory
Effects of Products of Coal and Oil Shale Conversion on Cell Cycle Kinetics and Chromatin Structure	Tobey	Los Alamos Scientific Laboratory
Development and Use of Differentiated Cell Culture Systems for the Evaluation of Toxicological Agents	Gerschenson	UCLA Laboratory of Nuclear Medicine and Radiation Biology
Development of Permanent Epithelial Cell Line for Studying Toxic/Carcinogenic Effects of Environmental Carcinogens	Selkirk/Kenney	Oak Ridge National Laboratory
Development of Method for Utilizing Teeth as an Indicator of Tissue Dose for Trace and Heavy Metals	Stang	Brookhaven National Laboratory

KING-MUIR CATEGORY #2 (Concluded)

PROJECT	PRINCIPAL INVESTIGATOR	AFFILIATION
Development of Nonmammalian (Fish) Model for Quantitative Evaluation of Carcinogenicity of Coal Conversion Products	Setlow	Brookhaven National Laboratory
Develop Tracheal Graft Model System for Evaluating Toxicity and Carcinogenicity of Polycyclic Hydrocarbons	Greisemer/Pal	Oak Ridge National Laboratory
Computer In Vivo Detection of Mutations in Somatic and Germinal Cells	Malling	NIEHS
Development of a System for Detecting Lethal Mutations in Mice	Roderick	The Jackson Laboratory
Development of a New Mouse Strain to Maximize the Sensitivity of a Point Mutation Assay	Roderick	The Jackson Laboratory
Amplification of Point Mutation System: Characterization of Mouse Esterases by Isoelectric Focusing	Allen	Medical University of South Carolina
Development of a Polygenic Assay for Point Mutations in Mice	Crenshaw	Georgia Institute of Technology
Detection of Point Mutations in Somatic Cells	Nute	University of Washington
Development of Faster, More Efficient and Less Costly Methods for Determining Teratogenic Changes	Johnson	Research Triangle Institute
Mutagenesis in Cultured Lymphocytes	Bloom	Columbia University
Multiple Loci Screen for Mutations in Mammalian Cells	Siciliano	University of Texas Cancer Center
Development of DNA Repair for Monitoring Human Health	Mitchell	Stanford Research Institute
A Modified Host-Mediated Assay Using Human Cells	Huang	New York State Department of Health
Developmental Toxicology Indicators	Dixon	NIEHS
Carcinogenesis of Fossil Fuel Related Combustion Products	Nettesheim	NIEHS
Validation of Short-Term Tests for Mutagenicity as Predictors of Potential Carcinogenic Activity	de Serres	NIEHS
DNA Repair Capacity and the Mutagenic and Carcinogenic Effects of Chemicals in Eukaryotes	de Serres	NIEHS
Mutagenic Mechanisms	Drake	-
Aneuploidy Workshop	de Serres	NIEHS

KING-MUIR CATEGORY #3

PROJECT	PRINCIPAL INVESTIGATOR	AFFILIATION
Effects of Environmental Pollutants in Relation to Age: Toxicity of Compounds Emitted from Coal Gasification	Kostial	Institute for Medical Research and Occupational Health, Zagreb, Yugoslavia
Scanning Electron Microscopic Examination of the Effects of Air Pollutants on Pulmonary Systems	Aranyi	IIT Research Institute
Studies on the Relationship between Carcinogen Metabolism in the Alveolar Macrophage	Garrett	Northrop Services
Investigation of Effects of Prolonged Inhalation of Nickel-Enriched Fly Ash in Syrian Golden Hamsters	Wehner	Battelle, Pacific Northwest Laboratories
Comparative Toxicological Assessment of Fly Ash from Western and Eastern Coal	-	Huntington Research Corporation
The Effects of NO_2 Exposure on the Disposition and Metabolism of Certain Endogenous Antioxidants of the Mammalian System	Lunan/Brandt	Stanford Research Institute
Interactions of Various Pollutants on Causation of Pulmonary Disease	Fenters/Ehrlich	IIT Research Institute
Effects of Alternate Energy Material on Whole Animal Carcinogenesis and Support of Fibrous Amphiboles	-	-
Effect of Trace Elements and Heavy Metal on the Detoxification of Sulfite by Sulfite Oxidase	-	Duke University
Deposition, Retention and Dosimetry of Inhaled Reaction Products Which May Result from SO_2 Particle Reactions	Snipes	Lovelace Foundation
Metabolism of Inhaled Trace Metal Effluents from Combustion Processes	Cuddihy	Lovelace Foundation
Influence of Diet on the Gastrointestinal Absorption of Cadmium	Walburg	University of Tennessee
Synthesis of Labeled Organic and Organometallic Compounds for Use in Metabolism and Catabolism Studies	Wolf	Brookhaven National Laboratory
Metabolism and Disposition of Selected Radio-labelled Hydrocarbons and Some of Their Chemically Reactive Epoxides by the Isolated, Perfused Rabbit Lung and by Solubilized, Reconstituted Pulmonary Biotransformation System	Bend	NIEHS
Environmental Teratology Information Center (ETIC)	Wassom	Oak Ridge National Laboratory
Regulation of Neural Distribution of Lead	O'Tauma	University of North Carolina
Function of Metallothionein in Heavy Metal Metabolism	Brady	University of South Dakota
Mechanisms of Heavy Metal Toxicity	Woods	NIEHS
Effects of Microwave Radiation on the Nervous System	Lovely	University of Washington

KING-MUIR CATEGORY #3 (Concluded)

PROJECT	PRINCIPAL INVESTIGATOR	AFFILIATION
Biological Effects of 60-Hertz Electric Fields	Marino	Research Foundation of SUNY
Respiratory Tract Deposition Models	Raabe	Lovelace Foundation
Respiratory Tract Deposition of Inhaled Aerosols	Yu	State University of New York at Buffalo
Factors Affecting Irritant Potency of Gases and Aerosols	Amdur	Harvard School of Public Health
Compartmental Models for Body Burden of Pollutants	Marcus	University of Maryland
Trace Element Deposition in Ambient Aerosol Inhalation	Winchester	Florida State University
Regional Deposition of Inhaled Particles in Man	Lippman	New York University Medical Center
Development of NMR Spectroscopic Methods for Characterizing Specific Bonding (Electronic and Covalent Bonding) Modes of Organics and Inorganics Associated with Nonnuclear Energy Technologies	McKinney	NIEHS
Development of the Probability Matched Gas Chromatographic Mass Spectrographic System to Screen Biological Tissue from Mothers and Newborn Infants for Energy-Related Chemicals in the Environment	Dixon	-
Biochemical Mechanisms of Pulmonary Injury	Hook/Eling	-
The Interaction of Lead with Body Tissues and Fluids	McKinney	-
Photodegradation of Absorbed Polycyclic Arenes	Daisey	-
Interaction between Light and Environmental Agents	-	-
Lung Cell Conversion of PAH	Bend	-
Pharmacology of PCBs	Matthew	-
Pharmacokinetics of Pulmonary Uptake and Metabolism	Wilson	-
Relationship of Metabolism, Fate, and Toxicology of Particulates and Organic Compounds	Bruckner	NIOSH
Nucleation Properties of Respirable Coal Dust	Schoengerdt	Colorado School of Mines
Cellular Response to Coal In Vitro	Christian	University of Cincinnati
V/Q in Occupational Lung Disease--Basic Development	Massaro	University of Wisconsin

KING-MUIR CATEGORY #4

PROJECT	PRINCIPAL INVESTIGATOR	AFFILIATION
The Effect of Low Levels of Sulfuric Acid Mist Expsosure on Human Pulmonary Function	Horvath	University of California
Effects of NO_2 on Pulmonary Function in Human Subjects with Asthma and Chronic Bronchitis	Kerr	University of Maryland
Effect of Respirable Sulfates and H_2SO_4 Mist upon Respiratory Function in Normal Human Subjects	Kerr	University of Maryland
Determination of the Effects of Material from Alternate Energy Sources on Upper Respiratory Tract Clearance Mechanisms	Adalis	Ball State University
Chemical Repository for Alternate Energy Source Material	Guerin	Oak Ridge National Laboratory
Studies of Health Effects Resulting from Increased Indoor Air Pollution from Energy Conservation Strategies Based on Current Activities	Moschandreas	Geomet
Model for Measuring the Health Impact from Changing Levels of Ambient Air Pollution	Carnow	University of Illinois
Determination of Toxicity from Coal Gasification Products Using Cellular Model Systems	Zarkower	Pennsylvania State University
Tracheal Organ Culture as Air Pollution Damage Indicator	Schiff/Ehrlich	IIT Research Institute
Effect of Material from Alternate Energy Sources on Whole Animal Defense System	Gause	Southwest Research Foundation
Effects of Conventional and Advanced Coal Conversion By-Products on the Pulmonary System	Aranyi	IIT Research Institute
Effects of Chronic or Intermittent Exposure to Respirable Particles and Mists in Mouse Pulmonary Infectivity Model	Ehrlich/Bradof/Fenters	IIT Research Institute
Evaluation of Neonate Squirrel Monkeys Receiving Tritiated Water throughout Gestation	Jones	Stanford Research Institute
Investigation of the Neoplastic and Life Space Effects of Potentially Sensitive Populations of Rats Chronically Exposed to Tritiated Water	-	Dawson Research Corporation
Effect of Pollutants from Energy Consumption and Environmental Trace Metals on Lung Metabolism	Mustafa	UCLA School of Medicine
Study of Metabolic and Physiologic Measurements in Populations with Long-Term Exposure to Pollution from Coal Combustion	Mostardi	University of Akron
Determination of Carcinogenic, Mutagenic, and Teratogenic Potential of Five Compounds Generated from Coal Conversion and Utilization to Which Man is Exposed Orally and by Inhalation	Hart	Litton Bionetics
Epidemiologic Study of People Using Water Supplies Originating in Areas Used for Coal Extraction (Western and Eastern)	-	-

KING-MUIR CATEGORY #4 (Continued)

PROJECT	PRINCIPAL INVESTIGATOR	AFFILIATION
Evaluate the Influence of Inhalation of Acid Aerosols, H_2SO_4, SO_3, HNO_3 and Particulates on Production of Chronic Lung Disease in Rats, Guinea Pigs and Primates	Tyler	University of California
Effects of SO_x Pollutants on Respiratory Function, Particle Deposition and Bronchial Clearance	Lippman	New York University
CLEANS/CLEVER:		
Operation and Maintenance	-	Rockwell International
Quality Control for Assessment of Human Exposure	Wilcox	Northrop Services
Aerosol Addition to CLEANS	-	Environmental Research and Technology
Stationary and Mobile Facilities for Study of Health Effects of Environmental Contaminants (CLEANS/CLEVER)	Marsh	Computer Science Corporation
CHAMP:		
Continuous Air Quality Monitoring for Community Health Studies	Raphael	Rockwell International
Addition of Mobile Air Monitoring Field Stations and Portable Air Pollution Monitors to CHAMP System	Raphael	Rockwell International
Operation, Calibration and Maintenance of Total CHAMP System	Raphael	Rockwell International
Operation and Maintenance of the Community Health Air Monitoring Program	Sullivan	Xonics, Inc.
The Effect of Whole Animal Exposure to Acid Mists on Pulmonary Metabolism of Benzo(a)pyrene in the Isolated Perfused Lung Model	Warshawsky	University of California
An Environmental Health Study of Lead in Teeth	Wilkinson	Delaware State College
Maintain CHESS Stations and Collect Data in Chattanooga Area	Decker	Research Triangle Institute
Human Biochemical and Physiologic Response to Acute Photochemical Air Pollution Exposures	Flesh	Copley International
The Effects of Low Levels of NO_3, O_3, and Ambient Air Separately and in Combination on Cardiac, Pulmonary, and Peripheral Circulatory Function in Adult Males in Response to Heat Stress at Rest and During Moderate Exercise	-	University of California
Feasibility Study on the Mortality Effects of Deterioration in Air Quality Due to Fossil Fuel Power Generation	Shy	University of North Carolina
Evaluation and Research of Methodology for National Environmental Specimen Bank	LaFleur/Rook	National Bureau of Standards
Hematologic and Mutagenic Effects of Arsine	-	New York University Medical Center

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KING-MUIR CATEGORY #4 (Continued)

PROJECT	PRINCIPAL INVESTIGATOR	AFFILIATION
Cytogenetic Studies of Lung Cells Following Inhalation of Fly Ash, Chemical Mutagens and Effluents from Power-Related Industry	Brooks	Lovelace Foundation
Factors Influencing Cross-Placental Transfer and Teratogenicity of Metallic Pollutants	Hackett	Battelle, Pacific Northwest Laboratory
Genetic Effects from Electric Fields at the Chromosomal Level of *Drosophila*	Hungate	Battelle, Pacific Northwest Laboratory
Use of the Mouse Specific-Locus Method to Quantify the Gene Mutation Hazard from Mutagens Associated with Nonnuclear Energy Technologies	Russell	Oak Ridge National Laboratory
Screening for the Mutagenicity and Carcinogenicity of Energy-Related Pollutants	Hsie	Oak Ridge National Laboratory
The Use of Selected Teratogenic Test Systems to Identify Hazardous Agents Associated with Nonnuclear Energy Technologies, and to Determine Effective Levels of Such Agents	Russell	Oak Ridge National Laboratory
The Mouse Oocyte System as a Monitor of Chemical Toxicity	Dobson	Lawrence Livermore Laboratory
Teratogenic and Mutagenic Effects of Trace Metals and Carcinogenic Hydrocarbons on Cultured Mammalian Cells	de Vellis	UCLA Laboratory of Nuclear Medicine and Radiation Biology
Evaluate the Effect of Low Level Chronic Radiation on Mammalian Brain Development Over Several Generations	Zamenhof	UCLA Laboratory of Nuclear Medicine and Radiation Biology
Combined Effects of Acute and Chronic Exposure to CO, NO_2, SO_2, and Fly Ash	Craig	Battelle, Pacific Northwest Laboratory
Effects of Sulfur Pollutants on Lung Physiology and Biochemistry	Loscutoff	Battelle, Pacific Northwest Laboratory
Effect of Acid Sulfate Particles and SO_2 on the Bacterial, Anti-Viral and Particle Clearance Mechanism in the Lung	Hahn	Lovelace Foundation
Cardiopulmonary Injury and Repair after Inhaled Acid Sulfate Aerosols	Mauderly	Lovelace Foundation
Effects of Carbon Monoxide, Hydrogen Sulfide and Other Energy Products on Neurons in Tissue Culture	Tobias	Lawrence Livermore Laboratory
Interaction of Atmospheric Contaminants with Respiratory Structure and Receptors at Both Biochemical and Functional Levels	Morrow	University of Rochester Medical School
Temporal Aspects of Tumor Response to Individual and Mixed Carcinogen Exposure	Albert	New York University
The Role of Irritant Gases on the Susceptibility of Respiratory Tract Epithelium to Tumor Induction	Creasia/Nettlesheim	Oak Ridge National Laboratory
Organ Culture Studies with Tracheal Mucosa Pre-Exposed *In Vivo* to Polycyclic Hydrocarbons	Marchok	Oak Ridge National Laboratory

KING-MUIR CATEGORY #4 (Continued)

PROJECT	PRINCIPAL INVESTIGATOR	AFFILIATION
The Influence of Irritant Gases on Lung Tumor Induction in Mice Exposed to Urethane	Jones/White	Lawrence Livermore Laboratory
Multi-Mode Scanning Electron Microscopic Analysis of Individual Pollutant Particles in Lung	Hayes	Lawrence Livermore Laboratory
The Role of 1,2-Benzanthracene in Enhancing Hepatic Tumor Development in Rats	Peraino	Argonne National Laboratory
Animal Toxicology Studies of Effluent from Low BTU Gasifiers	-	-
Animal Toxicology Studies of H-Coal Liquefaction Operations	-	-
Effects of Environmental Agents on Male and Female Reproductive Tract Function	Davis	Endocrine Labs of Madison
Effects of 60-Hz Fields on the Mammalian Central Nervous System	Adey	UCLA
Respiratory and Cardiovascular Functions in Pollutant-Exposed Animals	VanStee	NIEHS
Effects of Gestational Exposure	Staples	NIEHS
Arsine Toxicity: A Potential Environmental Hazard	Goldstein	New York University Medical Center
Lead Toxicity and Energy Metabolism in Immature Brain	Holtzman	Stanford University
Binding of Methyl Mercury, an Environmental Hazard, with DNA	Maki	University of California at Davis
Neurochemical Correlates of Behavioral Toxicology	Wilson	NIEHS
Neurotoxicological Effects of Hexabrominated Biphenyls	Tilson	NIEHS
The Etiology of Pica in the Rat	Mitchell	NIEHS
Chemical and Environmental Mutagen Studies Utilizing the Tradescantia Test System	Van't Hof/Sparrow	Brookhaven National Laboratory
Compilation and Tabular Abstraction of Literature on Mutagenic Effects of Energy-Related Pollutants (EMIC)	Wassom	Oak Ridge National Laboratory
Electrophoresis of Mouse Tissue: Testing of Offspring after Parental Treatment with Energy-Related Pollutants:	Johnson	Research Triangle Institute
Electrophoretic Mobility Mutation Analysis in Mammals	Valcovic	NIEHS
Chemically Induced Mutations at Biochemical Loci in Mice	Johnson	NIEHS
Monitoring Mutagens (Clastogens) with Mammalian Chromosomes	Hsu	University of Texas Cancer Center
Risk Assessment for Environmental Carcinogens	Hoel	NIEHS
Development of Statistical Methodology for Low Dose Extrapolation	Hoel/Crump	NIEHS

KING-MUIR CATEGORY #4 (Continued)

PROJECT	PRINCIPAL INVESTIGATOR	AFFILIATION
Species-to-Species Carcinogenesis Extrapolation	Williams	American Health Foundation
Statistical Studies of Problems of Health and Biology	Neyman	University of California
Extrapolation of Polychlorinated Biphenyl Deposition	Siple	University of Arizona
Statistical Development of Multistage Carcinogenesis Models	-	NIEHS
Low Dose Toxicological Estimation	Hoel	NIEHS
The Effects of Heavy Metals on Neurotransmitter Translocation	Bondy	-
Lifelong Assessment of the Behavioral Effects of Prenatal Exposure to Heavy Metals	Tilson	-
Lifelong Assessment of the Behavioral Effects of Prenatal Exposure to Microwaves	Mitchell	-
Pathogenic Mechanisms in the Development of Emphysema and Pneumoconiosis	Brody/Plopper	-
Biology and Pathobiology of Pulmonary Epithelial Cells	Wu/DiAugustine	-
Effects of Exposure to Selected Industrial Hydrocarbon Solvents on Polycyclic Hydrocarbon Metabolism and Toxicity in Lungs	Bend	-
Childhood Health Effects of PCBs	Rogan/McKinney/Matthews	-
Assessment of Energy Occupational Safety and Health Problems:	Wagner/Knowles	NIOSH
Management and Operation of a Research Program in Support of the Western Area Occupational Health Laboratory	Couvillon	University of Utah Research Institute
Enumeration of Energy Occupational Health Problems	Wagner	NIOSH
Quick Response Evaluation of Energy-Related Occupational Safety and Health Problems	-	Stanford Research Institute
Conduct Oil Shale Worker Studies:	Regen/Costello/Jones	NIOSH
Mortality and Morbidity among Oil Shale Workers	Gilliam	NIOSH
Study of Health Effects of Oil Shale Workers	-	University of Utah Research Institute
Health Effects--Oil Shale Workers--Epidemiology	Costello	NIOSH
Health Effects--Oil Shale Workers--Industrial Hygiene	Jones	NIOSH

KING-MUIR CATEGORY #4 (Continued)

PROJECT	PRINCIPAL INVESTIGATOR	AFFILIATION
Conduct Coal Gasification and Liquefaction Worker Studies:	Knowles/Hearl/Selevan	NIOSH
Industrial Hygiene Characterization of Coal Gasification Pilot Plants	-	The Bendix Corporation
Coal Liquefaction and Gasification Mortality Study	Selevan	NIOSH
Conduct Coal Liquefaction and Gasification Worker Health Effects Conference	-	Office of Naval Research
Conduct Studies of Occupational Exposures to Insulation Materials:	Dement/Bayless/Palmer	NIOSH
Industrial Hygiene Studies of Mineral Wool Exposures	-	Stanford Research Institute
Mineral Wool and Clay Fiber Mortality Study	Bayless	NIOSH
Mineral Wool Fibers--Medical Aspects	Palmer	NIOSH
Mortality and Industrial Hygiene Study of Mineral Wool Workers	Zumwalde	NIOSH
Mortality Study of Small Fibrous Glass Workers	Bayless	NIOSH
Mortality and Industrial Hygiene Study of Clay Fibers Workers	Ness/Zumwalde	NIOSH
Conduct Studies of Occupational Exposure to Sulfuric Acid, Sulfur Dioxide, Sulfates, Nitric Acid, Nitrogen Dioxide, and Nitrates:		
Occupational Exposure to Sulfuric Acid and Sulfates--Environmental	Cassady	NIOSH
Occupational Exposure to H_2SO_4 and Sulfates--Mortality	Selevan	NIOSH
Study of SO_x/NO_x--Epidemiology	Gamble	NIOSH
Study of SO_x/NO_x--Industrial Hygiene	Jones	NIOSH
Mortality and Industrial Hygiene Study of H_2SO_4 and Sulfate Workers	Cassady	NIOSH
Conduct a Safety Study of Energy Industries:	-	The Bendix Corporation
Assessing Safety in Fossil Fuel Electric Power Generating Plant	-	The Bendix Corporation
Conduct Studies of TVA Workers:	-	TVA
Memorandum of Understanding Between NIOSH and TVA	-	TVA
Epidemiological Mortality Study of TVA Employees	Ortmeyer	NIOSH
Industrial Hygiene Studies of TVA Workers in Coal-Fired Power Plant	-	-

KING-MUIR CATEGORY #4 (Concluded)

PROJECT	PRINCIPAL INVESTIGATOR	AFFILIATION
Conduct an Epidemiology Study of Divers:	Costello	NIOSH
Medical Study of Divers (Morbidity and Mortality)	-	-
Conduct Solar Energy Workers Study	-	-
Coal Cleaning Worker Studies	-	-
Petroleum Production Worker Studies	-	-
Respiratory Effects of Insulation Materials--Inhalation Effects	-	-
Diesel Exhaust and Coal Dust Interaction (Diesel Exhaust/Coal Dust Animal Exposure Studies)	-	-
Mining Worker Studies	-	-

KING-MUIR CATEGORY #5

PROJECT	PRINCIPAL INVESTIGATOR	AFFILIATION
Chemical and Molecular Interactions of Pollutants with Key Biological Molecules	Danyluk	**Argonne National Laboratory**
Molecular Damage to DNA and Proteins Caused by Hazardous Metals, Metal Ions, and Organic Compounds Associated with Coal and Oil Shale Technologies	Ward	**UCLA Laboratory of Nuclear Medicine and Radiation Biology**
The Study of Autoxidation of Lipids of Biomembranes and of Lung Surfactants Initiated by Oxidative Pollutants and Its Inhibition by Antioxidants	Mead	**UCLA Laboratory of Nuclear Medicine and Radiation Biology**
Effect of Hydrocarbons, SO_2, and Related Fossil Fuel Pollutants on the Biochemical Properties of Lung Membranes during Development	Snyder	**Oak Ridge Associated Universities**
Effects of Hazardous Agents Associated with Coal and Oil Shale Technologies on Informational and Regulatory Macromolecules of Mammalian Cells	Enger	**Los Alamos Scientific Laboratory**
Damage to DNA Synthesis by Trace Metals and Hydrocarbons	Popenoe	**Brookhaven National Laboratory**
Molecular Mechanisms of Chemical Carcinogenesis	Calvin	**Lawrence Livermore Laboratory**
Characterization and Control of Frameshift Mutation	Tinoco	**Lawrence Livermore Laboratory**
Characterization of Damage to DNA Caused by Chemical Agents: Emphasis on Synergistic Effects in Combination with Sunlight	Rahn	**Oak Ridge National Laboratory**
Regulatory Processes in Damaged Cells	Kenney	**Oak Ridge National Laboratory**
Damage and Repair to DNA in Specific Germ Cell Stages of Mammals Following In Vivo Exposure to Products Associated with Coal Conversion and Utilization	Sega	**Oak Ridge National Laboratory**
Interactions between Damage (and Repair to Damage) Resulting from Hazardous Agents Associated with Coal and Oil Shale Technologies and Ultraviolet Damage	Setlow	**Brookhaven National Laboratory**
Damage-Repair Studies Related to Cell Function and Molecular Processes	Elkind	**Argonne National Laboratory**
Repair of DNA Treated with Irradiation and Chemical Carcinogens	Goldthwait	**Case Western Reserve Institute**
Biological Damage Processes of Hydrocarbons: Molecular Activation and Binding Evaluated by EPR	Borg	**Brookhaven National Laboratory**
Reparative and Adaptive Mechanisms in Respiratory Systems of Rodents and Monkeys Exposed to Sulfur Compounds and Particulates	Goldman	**University of California, Davis**

KING-MUIR CATEGORY #5 (Continued)

PROJECT	PRINCIPAL INVESTIGATOR	AFFILIATION
Lung Cell Injury and Repair after Inhalation Exposure to Particulate Acid Sulfates	Slauson	Lovelace Foundation
Alveolar Clearance of Inhaled Metal Oxide	Sanders	Battelle, Pacific Northwest Laboratory
Effects of Chemical Toxicants Associated with the Production and Consumption of Fuel on the Physiology and Pathophysiology of Phagocytic Cells	Skosey	Franklin McLean Memorial Research Institute, University of Chicago
Evaluation of the Mechanisms of Energy-Related Toxic Agents on the Mammalian Hematopoietic System Using Flow Microfluorometric Analysis	Steinkamp	Los Alamos Scientific Laboratory
Functional and Quantitative Changes in Immunocompetent Cells, Induced by a Carcinogen Product of Coal and Oil Utilization	Jaroslow	Argonne National Laboratory
Environmental Carcinogenic Studies in a Subhuman Primate	Genzozian	Oak Ridge Associated Universities
To Determine the Processes by Which Laboratory Mammals Recover from Damage by Exposure to Pollutants Associated with Coal Gasification and Shale Distillation with Emphasis on the Sequence of Events Occurring in the Immune System	Smith	Los Alamos Scientific Laboratory
Evaluation of the Dose-Effect Relationships for Immune Response to Biologically Active Agents Associated with Coal Gasification Technologies	Cram	Los Alamos Scientific Laboratory
Therapy of Nonradioactive Toxic Metal Compounds	Lindenbaum	Argonne National Laboratory
Effects of Pollutants upon Alveolar Macrophage	Rowlands	Southwest Foundation for Research and Development
Can Vitamin E or Lipid Alter NO_2 or O_3 Toxicity in Lung?	Menzel	Duke University Medical Center
Vitamin A Effect on Lung Cell Kinetics after NO_2	Kim	Michigan State University
The Interaction of Cadmium with the Pulmonary Alveolar Macrophage	Hart	University of Vermont
Pulmonary Effects of Environmental Oxidant Pollutants	Dungworth	University of California, Davis
Environmental Cellular Toxicology Program	Wenzel	University of Kansas
The Interaction of Chemical Agents Present in Oil Shale with Biological Systems	Chignell	NIEHS
The Effect of NO_x Air Pollutants on Membranes	Chignell	NIEHS
Identification of Markers for Preneoplasia in Respiratory Epithelium	Nettesheim	-

KING-MUIR CATEGORY #5 (Concluded)

PROJECT	PRINCIPAL INVESTIGATOR	AFFILIATION
Identification of Peripheral and Central Receptor Mechanisms Mediating the Effects of Microwave Radiation on Brain Activity	Wilson	-
Effects of Microwave Radiation on Neural Response and the Central Nervous System	McRee	-
Recommended Standards for Coal Gasification and Liquefaction Plants	-	Enviro Control, Inc.
Develop Medical Protocols for Energy Industries	-	-
Conduct Study of Recirculation of Exhaust Air:		
Development of Criteria for the Recirculation of Industrial Exhaust Air	-	Arthur D. Little, Inc.
Recirculating Exhaust Air Symposium	-	Research Triangle Institute
Validation of Criteria for Recirculation	-	Envirex
Validation of Criteria for Recirculation	-	Arthur D. Little, Inc.
Develop a Criteria Document for Occupational Exposure to Microwave and RF Radiation	-	-
Study Work Practice Needed to Protect Alaskan Pipeline Workers from Cold Stress	Jensen	NIOSH
Develop Countermeasures to Protect Divers Involved in Offshore Oil Exploration:	Fairchild	NIOSH
Development of a National Plan for the Safety and Health of Divers in the Quest for Sub-Sea Energy	Shelling	Undersea Medical Society
Develop Recommended Medical and Operating Standards for Divers	Hamilton	Tarrytown Labs, Ltd.

[a] Not identified